Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende larotrectinib til behandling af NTRK-fusion-positiv kræft

Vers. 1.0

Bilagsoversigt

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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Larotrectinib

NTRK-fusion-positiv kræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
BSC	*Best supportive care*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
GBP	*British pound*
IHC	*Immunohistochemistry*
KM	Kaplan-Meier
NTRK	Neurotrofisk tyrosinreceptorkinase
NGS	*Next-generation sequencing*
OS	Overlevelse
PD	Progredieret overlevelse
PFS	Progressionsfri overlevelse
RCT	*Randomized controlled trial*
RDI	*Relativ dosisintensitet*
TTD	*Time to Treatment Discontinuation*
SAIP	Sygehusapotekernes indkøbspris
SmPC	*Summary of Product Characteristics*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet finder mest sandsynligt, er de inkrementelle omkostninger for larotrectinib ca. [redacted] DKK pr. patient for voksne og ca. [redacted] DKK pr. patient for børn sammenlignet med *best supportive care* (BSC). Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. 1,7 mio. DKK pr. patient for voksne og ca. 2,0 mio. DKK pr. patient for børn.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for larotrectinib, men fordi udregningen af lægemiddelomkostningerne er baseret på meget usikre ekstrapolerede kurver, er resultatet usikkert. Dette ses i følsomhedsanalyserne, der viser, at den valgte parametriske funktion til ekstrapolering af progressionsfri overlevelse (PFS) og overlevelse (OS) har stor betydning for resultatet.

Desuden er der usikkerhed vedr. de gennemsnitlige testomkostninger pr. patient. Testomkostningerne afhænger af, hvilken test der anvendes, samt hvor mange NTRK-fusion-positive patienter der identificeres. Følsomhedsanalyserne viser, at det har stor betydning, hvorvidt der testes initialt med immunhistokemi (HC) eller *next-generation sequencing* (NGS), mens at antallet af patienter, der identificeres, har mindre betydning for det endelige resultat.

Ansøger har ikke inkluderet lægemiddelomkostninger for patienter i behandling med BSC i modellen. Dette kan potentielt være en underestimering af omkostningerne ved nuværende behandling med BSC, da patienterne sandsynligvis vil modtage symptomlindrende behandling, og derved vil de inkrementelle omkostninger være overestimerede. Denne usikkerhed er dog svær at kvantificere.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af larotrectinib som mulig standardbehandling vil være ca. [redacted] DKK for voksne i år 5 og ca. [redacted] DKK for børn. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 28,9 DKK for voksne i år 5 og ca. 12,3 mio. DKK for børn.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af larotrectinib som mulig standardbehandling på danske hospitaler til NTRK-fusion-positiv kræft.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bayer A/S. Vi modtog ansøgningen den 19. marts 2021.

3.1 Patientpopulation

Forekomsten af kræft i Danmark er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000, lidt flere mænd end kvinder. Den største andel af nye kræfttilfælde er i den ældre del af befolkningen. 2/3 af alle nye kræfttilfælde er hos personer over 60 år. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [1].

Selvom kræft er sjælden hos børn (under 18 år), er det den næst hyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 200 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [1]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [2].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, NTRK1, NTRK2 og NTRK3, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, koder for Trk-fusionsproteiner, som kan medføre ukontrolleret Trk-signalering og dermed tumorvækst [3,4]. NTRK-fusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-fusioner. NTRK-fusioners hyppighed i forskellige kræftformer er angivet i tabellen nedenfor. Dette skal dog tages med forbehold for de ovennævnte forskelle.

Tabel 3. Oversigt over frekvens for NTRK-fusion ved forskellige kræftformer

Kræftform	Frekvens for NTRK-fusion
Infantil fibrosarkom	Omkring 100 % [5,6]
Sekretorisk karcinom i både spytkirtel og bryst	Omkring 100 % [5,6]
Kræfttyper i luftveje, fordøjelseskanal, bryst og hjerne	< 5 % [5,6]
Lungekræft, kolorektalkræft, modermærkekræft og brystkræft	0,1-1 % [7]

Fagudvalget skønner, at mellem 10 og 40 patienter (voksne og børn) årligt er kandidater til behandlingen med larotrectinib i Danmark.

Antallet af patienter er dog usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og dels er larotrectinib først indiceret, når øvrige muligheder for behandling er udtømte. Derfor skal et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer.

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af larotrectinib på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvad er den kliniske merværdi af larotrectinib til behandling af voksne med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

Klinisk spørgsmål 2:

Hvad er den kliniske merværdi af larotrectinib til behandling af børn med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for larotrectinib sammenlignet med *Best Supportive Care* (BSC). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt. Ansøger har indsendt en mixture-cure-model samt en parametrisk partitioned survival-model. Ansøger har anvendt mixture-cure-modellen som primær analyse, såkaldt ”base-case” og har anvendt partitioned survival-modellen som følsomhedsanalyse. Sekretariatet har valgt udelukkende at gennemgå og præsentere den parametriske partitioned survival-model, fordi ansøger ikke har formået at redegøre for de sundhedsøkonomiske antagelser bag deres mixture-cure-model herunder antagelser om transitionspunkter og andel kurerede, og det er derfor ikke muligt for sekretariatet at validere disse.

4.1 Antagelser og forudsætninger for model

Data for larotrectinib består af et kombineret datasæt af patienter fra single-arm-studierne LOXO, SCOUT og NAVIGATE, som ansøger refererer som "PAS" og "ePAS". Patienterne i "PAS" er de samme 55 patienter, som indgik i Drilon et al. 2018 [8]. Datasættet "ePAS" inkluderer yderligere patienter og er inddelt i forskellige datasæt med forskellige opfølgningstider. Det seneste datasæt "ePAS5" er data-on-file og har dataopfølgning frem til juli 2020. Ansøger anvender dette i deres omkostningsanalyse. I vurderingsrapporten er ePAS4, med dataopfølgning frem til juli 2019, anvendt.

[redacted]

Da ingen af disse studier direkte sammenligner larotrectinib med BSC, har ansøger valgt at foretage en naiv sammenligning med BSC, som, ansøger argumenterer for, kunne bestå af behandling med doxorubicin. Derfor anvender ansøger data fra doxorubicin-armen fra et prospektivt RCT, Judson et al. [9], som undersøger doxorubicin mod doxorubicin kombineret med ifosfamide til førstelinjebehandling af voksne patienter med bløddelssarkom. I dette studie er NTRK-status ukendt. Ansøger argumenterer for, at doxorubicin-armen i Judson et al. [9] kan være et relevant sammenligningsgrundlag for larotrectinib, da bløddelssarkom er den hyppigste tumortype i datasættet for larotrectinib. Judson et al. [9] indeholder kun voksne patienter, og derfor vælger ansøger at bruge PFS- og OS-data for Judson et al. [9] både i sammenligningen med larotrectinib for børn og voksne.

Medicinrådets vurdering af de anvendte studier og data

Medicinrådet accepterer ansøgers tilgang vedr. valg af studier og data, men fagudvalget bemærker, at doxorubicin har meget lidt relevans som klinisk sammenligningsgrundlag, da doxorubicin ikke bruges i dansk klinisk praksis, og data for doxorubicin kun anvendes perspektiverende i vurderingsrapporten vedr. larotrectinib.

4.1.1 Modelbeskrivelse

Her er en beskrivelse af den partioned survival-model, som Medicinrådet har valgt at basere sig på til at estimere omkostningerne forbundet med behandlingen med larotrectinib.

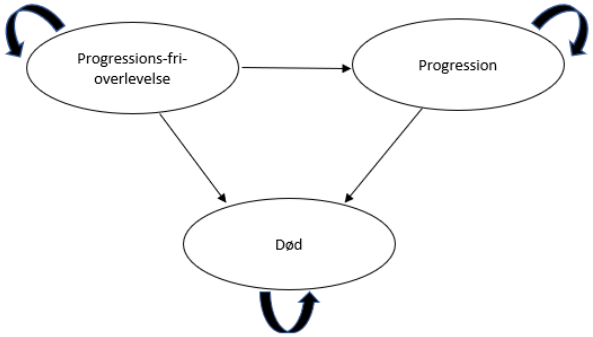
Modellen indeholder en række sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. Ansøgers model består af tre stadier: progressionsfri overlevelse, post-progression og død. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret time-to-event-data. Patientens tid i stadiet progressionsfri overlevelse bestemmes ud fra PFS-data fra "ePAS5" for larotrectinib og Judson et al. [9] for BSC. Fra progressionsfri overlevelse kan patienten bevæge sig videre til stadiet post-progression og til stadiet død.

Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression. Tiden, patienterne befinder sig i dette stadie, estimeres ligeledes ud fra PFS- og OS-data fra "ePAS5" for larotrectinib og Judson et al. [9] for BSC, som den andel af patienter, der hverken er i progressionfri overlevelse eller død. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død.

Andelen af patienter i stadiet død bliver estimeret ud fra OS-data "ePAS5" for larotrectinib og Judson et al. [9] for BSC.

Modellen har en cykluslængde på en uge.



Figur 1: Beskrivelse af modelstrukturen i omkostningsanalysen

Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i "ePAS5" og Judson et al. [9] er kortere end den anvendte tidshorisont.

[redacted]

Figur 2: PFS for voksne i behandling med larotrecitnib

Figur 3: PFS for børn i behandling med larotrecitnib

Figur 4: PFS både for børn og voksne i behandling med BSC

[redacted]

Figur 5: OS for voksne i behandling med larotrectinib

Figur 6: OS for børn i behandling med larotrectinib

Figur 7: OS for voksne og børn i behandling med BSC

[redacted] Ansøger antager, at BSC består af doxorubicin, og ansøger anvender en gennemsnitlig behandlingslængde på 126 dage, svarende til 6 cyklusser af 21 dage.

På baggrund af disse ekstrapoleringer har ansøger estimeret den gennemsnitlige tid, patienten befinder sig i modellens stadier.

Medicinrådets vurdering af ansøgers modelantagelser
Fagudvalget er blevet konsulteret og præsenteret for ovenstående kurver. Fagudvalget fremhæver meget klart, at disse kurver er behæftet med meget stor usikkerhed, og den kliniske plausibilitet af disse kurver er tvivlsom. Fagudvalget vurderer, at nogle børn vil blive langtidsoverlevere svarende til den ekstrapolerede OS-kurve, men den ekstrapolerede PFS-kurve udviser ikke et mønster af langtidsoverlevere. Fagudvalget vurderer derfor, at tolkning af disse kurver skal foretages med stort forbehold. Fagudvalget vurderer for voksne (klinisk spørgsmål 1), at [redacted] stemmer bedst overens med deres forventninger til patienternes forløb. Dette skyldes, at fagudvalget ikke forventer en hale af langtidsoverlevere ud fra deres kliniske erfaring og de tilgængelige data for larotrectinib.

Fagudvalget vurderer, at doxorubicin ikke er en relevant komparator, men kan ikke afvise, at den ekstrapolerede kurve for doxorubicin muligvis kan være en repræsentativ kurve for BSC. Medicinrådet fremhæver igen usikkerheden vedr. de ekstrapolerede kurver og fortolkningen af disse, idet doxorubicin ikke anvendes i dansk klinisk praksis, samt det forhold at Kaplan Meier-data anvendt til at foretage ekstrapoleringerne kun er baseret på voksne, men anvendes både i børn og voksne, hvilket Medicinrådet vurderer er urealistisk.

Der er mange usikkerheder vedr. alle disse ekstrapoleringer og resultatet af hovedanalysen kan derfor ikke stå alene. Som supplement til hovedanalysen udfører Medicinrådet en række følsomhedsanalyser af ekstrapoleringerne. Tolkning af hovedanalysen skal ske med forsigtighed, i relation til følsomhedsanalyserne.

For børn (klinisk spørgsmål 2) vælger sekretariatet at ekstrapolere med [redacted], idet antagelser bag den [redacted]. Slutteligt vælger sekretariatet at acceptere ansøgers antagelse om at anvende kurverne for doxorubicin fra Judson et al. [9] som proxy for BSC, selvom fagudvalget vurderer, at doxorubicin ikke anvendes i dansk klinisk praksis. I sundhedsøkonomiske analyser er det nødvendigt med kvantitative estimater og fagudvalget kan ikke afvise, at dataforløbet muligvis kan være repræsentativt for patienter i BSC, selvom det er tvivlsomt. Desuden vælger sekretariatet jf. afsnit 4.1 at ekskludere omkostninger til behandling med doxorubicin, som udgør størstedelen af omkostninger for BSC, og derfor spiller de ekstrapolerede kurver for BSC en mindre rolle.

Estimaterne anvendt i hovedanalysen er præsenteret i Tabel 1.

Tabel 1. Gennemsnitlig tid i behandling og i stadierne PFS, PD og OS

Behandling	Behandlingsvarighed [måneder]	PFS [måneder]	PD [måneder]	OS [måneder]
		Voksne		
Larotrectinib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
		Børn		
Larotrectinib	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

*Tid i behandling (ToT), progressionsfri overlevelse (PFS), samlet overlevelse (OS)

Som nævnt er disse ekstrapoleringer behæftet med betydelig usikkerhed, og derfor udføres følsomhedsanalyser, hvori den parametriske funktion anvendt til ekspoleringen varieres, samt en følsomhedsanalyse med de ekstrapolerede PFS- og OS-kurver fra Medicinrådets afrapporteringen vedr. entrectinib til NTRK-fusion-positiv kræft [10] anvendes.

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men Medicinrådet er ikke enig i de parametriske funktioner, ansøger har valgt til at ekstrapolere PFS og OS for larotrectinib. Medicinrådet vælger for larotrectinib at ekstrapolere PFS og OS for voksne med [redacted], mens PFS og OS ekstrapoleres med [redacted] for børn. Medicinrådet fremhæver, at usikkerheden forbundet med alle disse ekstrapoleringer er betydelige, og at fortolkning skal ske med forbehold.

4.1.2 Analyseperspektiv

I overensstemmelse med metoderne har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 80 år.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 4 % pr. år, mens omkostninger, der ligger efter år 35, bliver diskonteret med en rate på 3 % pr. år

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valgte tidshorisont, da ansøger argumenterer for, at den gennemsnitlige behandlingslængde ligger inden for denne tidshorisont. Det betyder ikke, at patienterne modtager behandling med larotrectinib i hele tidshorisonten, men at analysen opfanger alle direkte og afledte økonomiske forskelle mellem larotrectinib og BSC set over en tidshorisont på 80 år. Medicinrådet vælger at justere diskonteringsrenten til hhv. 3,5 % indtil år 35 og 2,5 % efter år 35, jf. Finansministeriets samfundsøkonomiske diskonteringsrente [11].

Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv, men vælger at justere diskonteringsrenten til 3,5% frem til år 35 og 2,5 % efter år 35.

4.2 Omkostninger

Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, bivirkningsomkostninger, testomkostninger og patientomkostninger.

Omkostningerne er cyklusbestemt, hvilket betyder, at omkostningerne påregnes for hver cyklus, patienten befinder sig i stadiet.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekets indkøbspris (AIP). Doser anvendt i ansøgers analyse er hentet i de respektive produkters produktresuméer (SmPC'er).

Behandling med larotrectinib:

100 mg to gange dagligt for voksne

100 mg/m^2 to gange om dagen (0,74 m^2 i gennemsnit) for børn

Best supportive care:

60 mg/m^2 doxorubicin hver 3. uge

Ansøger anvender den gennemsnitlige dosisintensitet på [redacted] for voksne og [redacted] for børn til at udregne dosis for larotrectinib. Ligeledes anvender ansøger det gennemsnitlige overfladeareal på 1,88 m^2 for voksne og 0,74 m^2 for børn til at udregne dosis for doxorubicin. Ansøger har kun inkluderet omkostninger til spild ved doxorubicin.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Fagudvalget vurderer, at ingen af patienterne i BSC vil modtage doxorubicin, men derimod at patienterne sandsynligvis vil modtage symptomlindrende behandling, og derfor ekskluderes omkostninger til doxorubicin. Symptomlindrende behandling er ikke inkluderet i modellen, hvilket bidrager til usikkerhed omkring resultatet. Usikkerheden peger dog i retning af underestimerede omkostninger for BSC og dermed overestimering af de inkrementelle omkostninger. Fagudvalget vurderer, at der vil opstå lægemiddelspild ved larotrectinib, i størrelsesorden én ekstra pakke larotrectinib. Dette tilføjer Medicinrådet til de samlede lægemiddelomkostninger.

Medicinrådet har udskiftet AIP med sygehusapotekets indkøbspris (SAIP), se Tabel 2.

Tabel 2. Anvendte lægemiddelpriser, SAIP, (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Larotrectinib	100 mg	56 stk.	[redacted]	Amgros
	25 mg	56 stk.	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men ekskluderer omkostninger til doxorubicin samt tilføjer omkostninger til spild ved larotrectinib.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger ved doxorubicin i BSC-armen i form af DRG-takster, men har ikke inkluderet administrationsomkostninger for larotrectinib, da larotrectinib administreres oralt, og ansøger antager, at en patient selv kan administrere det. Dette gælder både voksne og børn.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Medicinrådet accepterer ansøgers tilgang til estimering af administrationsomkostninger, men vælger at ekskludere omkostningerne til administration af doxorubicin, da fagudvalget vurderer, at ingen af patienterne i BSC vil modtage doxorubicin.

Medicinrådet accepterer ansøgers tilgang vedr. administrationsomkostninger, men ekskluderer alle administrationsomkostninger til doxorubicin i BSC.

Monitoreringsomkostning

Ansøger har inkluderet omkostninger i forbindelse med monitorering i form af DRG-takster. Ansøger antager, at progressionsfri patienter i forbindelse med monitorering modtager en CT-scanning hver 2. måned samt et besøg hos en onkolog hver måned, hvilket også inkluderer en leverfunktionstest og blodprøver. Derudover forventer ansøger, at der i gennemsnit vil være en indlæggelse og et palliativt forløb, men uddyber ikke, hvad disse udgiftsposter indeholder. For progredierede patienter antager ansøger, at patienterne vil modtage en CT-scanning hver 5. måned og et besøg hos en onkolog

hver 3. måned, hvilket også inkluderer en lever- og blodprøve. Disse omkostninger er identiske for både børn og voksne.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet vælger at acceptere ansøgers fremgangsmåde vedr. monitorering, men fagudvalget vurderer, at monitorering af progressionsfrie patienter sker én gang om måneden og gælder både CT-scanning og besøg hos onkolog, mens fagudvalget vurderer, at patienter ikke vil monitoreres efter progression. Medicinrådet ekskluderer omkostninger til indlæggelse og palliativ behandling, da ansøger ikke har redegjort for indholdet i disse udgifter. De anvendte omkostninger til monitorering er identiske for børn og voksne og kan ses i Tabel 3.

Tabel 3: Omkostninger til monitorering

	Månedlig frekvens [antal]	Enhedsomkostning [DKK]	Kilde
PFS			
Onkolog konsultation	1	1.316 DKK	Medicinrådets værdisætning af enhedsomkostninger
Blodprøver	1	352 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
Leverfunktion	1	60 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
CT-scanning	0,5	2.032 DKK	DRG 2021: 30PR06
Progredieret overlevelse			
Onkolog konsultation	0	1.316 DKK	Medicinrådets værdisætning af enhedsomkostninger
Blodprøver	0	352 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
Leverfunktion	0	60 DKK	Mikrobaseret tilgang med udgang i Rigshospitalets labportal
CT-scanning	0	2.032 DKK	DRG 2021: 30PR06

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men ekskluderer omkostninger til monitorering efter progression samt omkostninger til indlæggelse og palliativ behandling.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger til håndtering af bivirkninger ved både larotrectinib og BSC. Ansøgers model benytter frekvenser for uønskede hændelser (AE) af grad 3-4 som mål for bivirkningerne, men har kun inkluderet uønskede hændelser, hvor frekvensen er højere eller lig med 5 %. For larotrectinib har ansøger benyttet de rapporterede bivirkningsrater fra ePAS4, som også er inkluderet i Medicinrådets vurderingsrapport vedr. larotrectinib. For BSC har ansøger benyttet de rapporterede bivirkningsrater fra Judson et. Al [9]. Ansøger har dog takseret de samlede omkostninger til bivirkninger med 5.000 DKK årligt både for BSC og larotrectinib, men har ikke redegjort for, hvad disse omkostninger indeholder.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ikke ansøgers anvendte bivirkningsomkostning. For larotrectinib anvendes de respektive DRG-takster fremfor en samlet omkostning på 5.000. De anvendte bivirkningsomkostninger kan ses i Tabel 4. Bivirkningsomkostninger til doxorubicin ekskluderes, da det ikke anvendes som BSC i dansk klinisk praksis.

Tabel 4. Rapporterede bivirkningsfrekvenser ved behandling med larotrectinib samt enhedsomkostninger for bivirkningerne

	Larotrectinib [%]	Takst [DKK]	Kilde
		Voksne	
Anæmi	10	21.529	DRG2021: Gennemsnit af 16MA98 og 16MA05
Lymfocytopeni	7	3.114	DRG2021: 16MA98
Sepsis	5	42.770	DRG2021: 18MA01
Øget alanin-aminotransferaseniveau	5	0	Antagelse
		Børn	
Neutropeni	23	19.299	DRG2021: Gennemsnit af 16MA98 og 16MA03
Vægtøgning	10	0	Antagelse
Pyreksi	7	2.676	DRG2021: 18MA98
Anæmi	7	21.529	DRG2021: Gennemsnit af 16MA98 og 16MA05

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger, men erstatter bivirkningsomkostninger med DRG-takster samt ekskluderer bivirkningsomkostninger ved BSC.

Testomkostninger

Ansøger har inkluderet omkostninger til test for NTRK-fusion. Til estimering af denne omkostning antager ansøger, at der årligt er 30.000 patienter, der diagnosticeres med kræft. Af de 30.000 sorterer ansøger patienter fra, hvor forekomsten af NTRK er meget sjælden (f.eks. bryst-, prostata- og lymfekræft), og ender med 17.500 patienter, hvoraf ansøger antager, at 50 % vil udvikle uhelbredelig kræft. Dermed antager ansøger, at 8.750 patienter skal testes for NTRK-fusion. Ansøger antager, at alle patienter først testes med immunhistokemi (IHC) og derefter, for positive patienter, bekræftes dette med *next-generation sequencing* (NGS). Af de 8.750, som testes med IHC, antager ansøger, at 550 patienter vil teste positiv med IHC, mens NGS kun vil bekræfte NTRK-fusionen blandt 50 patienter. Ansøger takserer hhv. IHC og NGS med 550 DKK og 5.000 DKK per test. Ansøger deler de samlede testomkostninger blandt de 50 patienter med bekræftet NTRK, hvilket resulterer i en gennemsnitlig testomkostning på 151.250 DKK. Testomkostninger er kun inkluderet i sammenligningen med BSC for voksne og er inkluderet både på patienter i behandling med larotrectinib og BSC.

Medicinrådets vurdering af ansøgers antagelser vedr. testomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af testomkostninger, men Medicinrådet er uenige i det konkrete antal patienter, som forventeligt skal testes. Medicinrådet vurderer, ligesom i Medicinrådets vurdering vedr. entrectinib til NTRK-fusion positiv kræft [10], at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft, og at ca. 1/3 af disse vil udtømme øvrige behandlingsmuligheder, men stadig være i tilstrækkelig performancestatus til at modtage yderligere behandling. Det er således i ovenstående population, at man skal identificere de patienter, som kan være kandidater til behandling med larotrectinib. Af disse vurderer fagudvalget, at mellem 1.000 og 1.500 patienter vil have modtaget en test i tidligere behandlingsforløb, og derfor vurderer fagudvalget, at der skal testes mellem 1.500 og 2.000 patienter årligt for at finde de 10-40 patienter, som vil være kandidater til larotrectinib.

Fagudvalget vurderer, at patienter indledningsvist skal testes med IHC til en omkostning på ca. 600 DKK. Påvises NTRK-fusion ved IHC følges op med en NGS-test. IHC vil føre til nogle falsk positive prøver, hvilket betyder, at ca. 40 patienter vil skulle testes igen ved NGS, til en omkostning på ca. 5.000 DKK, for endeligt at identificere de patienter, som er kandidater til behandling med larotrectinib.

De samlede testomkostninger (1.500-2.000 x 600 + 40 x 5.000 = 1,1 - 1,4 mio. DKK) deles blandt de 20 bekræftede patienter med NTRK, som fagudvalget forventer i år 1 (10 børn og 10 voksne) og 30 (10 børn og 20 voksne) i år 2, jf. afsnit 4.1, hvilket resulterer i en gennemsnitlig testomkostning på 55.000-70.000 DKK i år 1 og 36.700-46.700 DKK i år 2. NTRK-fusion er hyppig blandt børn, og derfor vil det ikke være nødvendigt at teste ligeså mange børn for at finde de 10 kandidater. Af denne årsag vælger sekretariatet, ligesom ansøger, at ekskludere testomkostninger for børn samt at anvende en testomkostning på 55.000 DKK (gennemsnitlig ved 20 patienter) for voksne. Testomkostninger inkluderes kun for patienter i behandling med larotrectinib og ikke med BSC. Dette er konsistent med testomkostningerne anvendt i Medicinrådets vurdering af entrectinib til NTRK-fusion [10], men Medicinrådet fremhæver, at der er usikkerhed om testomkostninger, og

vælger derfor at foretage følsomhedsanalyser af testomkostninger, som er beskrevet i afsnit 4.3

4.2.3 Patientomkostninger

Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet, som beskrevet i afsnit 4.2.2, og inkluderer patientens effektive tid på hospitalet, ventetid og transporttid. Ansøger antager, at patienttiden udgør to timer ved CT-scanning, en time ved blodprøve og leverfunktionstest, og to timers besøg hos onkolog. Ansøger antager, at disse omkostninger er ens for både larotrectinib og BSC og for både børn og voksne.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger.*

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Medicinrådet accepterer ansøgers tilgang vedr. patient- og transportomkostninger, men reducerer patienttiden ved CT-scanning til 60 min., blod og leverfunktionstest til 30 min. og besøg hos onkolog til 30 min. Disse ændringer har minimal betydning for resultatet.

Ansøger har i sin analyse inkluderet omkostninger til andre symptomlindrende lægemidler (ondansetron, paracetamol, metoclopramid, dexamethason, oxycodon), men har ikke gjort antagelser, om hvorvidt disse udleveres på hospitalet eller købes af patienten i primærsektoren. Sekretariatet vælger at antage, at disse købes af patienten i primærsektoren, og dermed udgør en patientomkostning. Disse udgifter er meget små.

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostningerne, men vælger at reducere patienttiden ved CT-scanning, blodprøver, leverfunktionstest og besøg hos onkolog.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har kun udarbejdet en følsomhedsanalyse, hvor modelstrukturen ændres fra en mixture-cure-model til en parametrisk partioned survival-model, men har ikke foretaget yderligere følsomhedsanalyser.

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser
Medicinrådet vælger at anvende ansøgers partioned survival-model som hovedanalyse, og at udføre følgende følsomhedsanalyser:

Tabel 5. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Parametriske kurver fra entrectinib (kun muligt for voksne)	De ekstrapolerede kurver anvendt for PFS, OS og ToT i Medicinrådets afrapportering vedr. entrectinib til NTRK-positiv kræft [10] anvendes fremfor de ekstrapolerede kurver for larotrectinib. I dette scenarie antages det at larotrectinib og entrectinib har samme effekt, og prisen dermed er sammenlignelig.
Varierende parametrisk ekstrapolering af PFS- og OS-kurven for larotrectinib	[redacted]
Testomkostninger	Ingen testomkostninger
	Antages, at 2.000 patienter skal testes med IHC for at finde 20 voksne patienter, som kandiderer til behandling med larotrectinib
	Antages, at 1.500 patienter skal testes med NGS for at finde 20 voksne patienter (5.000 DKK per test) svarende til 375.000 DKK per patient

Medicinrådet accepterer ikke, at ansøger ikke har udført følsomhedsanalyser, og derfor vælger Medicinrådet selv at udføre følsomhedsanalyser af de mest usikre parametre.

4.4 Opsummering af basisantagelser

I Tabel 6 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	80 år	80 år
Diskonteringsrate	4 % for år ≤ 35	3,5 % for år ≤ 35
	3 % for år > 35	2,5 % for år > 35
Inkluderede omkostninger	Administrationsomkostninger	Administrationsomkostninger
	Monitoreringsomkostninger	Monitoreringsomkostninger
	Bivirkningsomkostninger	Bivirkningsomkostninger
	Testomkostninger	Testomkostninger
	Patient- og transportomkostninger	Patient- og transportomkostninger

Basisantagelser	Ansøger	Medicinrådet
Dosering	Larotrectinib: 100 mg to gange dagligt med RDI på [redacted] % for voksne 100 mg/m2 to gange dagligt med RDI på [redacted] % for børn BSC: 60 mg/m2 doxorubicin hver 3. uge. Gennemsnitlig 1,88 m2 for voksne og 0,74 m2 for børn	Larotrectinib: 100 mg to gange dagligt med RDI på [redacted] % for voksne 100 mg/m2 to gange dagligt med RDI på [redacted] % for børn BSC: Ingen behandling
Behandlingslængder		
Intervention:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Komparator:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Parametriske funktioner for PFS		
Intervention:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Komparator:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Parametriske funktioner for OS		
Intervention:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Komparator:		
Voksne	[redacted]	[redacted]
Børn	[redacted]	[redacted]
Inkludering af spild	Nej	Ja

Basisantagelser	Ansøger	Medicinrådet
Andre væsentlige antagelser	Gennemsnitlige testomkostninger på ca. [redacted] DKK for både larotrectinib og BSC	Gennemsnitlige testomkostninger på 55.000 DKK for larotrectinib og ingen testomkostninger for BSC
	Inkludering af bivirkningsomkostninger ved BSC	Ekskludering af bivirkningsomkostninger ved BSC

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers følsomhedsanalyse med undtagelse af de ændringer, der er gennemgået ovenfor.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK for voksne og ca. [redacted] for børn i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer de første 5 år af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 1,7 mio. DKK for voksne og ca. 2,0 mio. DKK for børn.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i Tabel 7 og Tabel 8.

Tabel 7. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC for voksne (klinisk spørgsmål 1), DKK, diskonterede tal

	Larotrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	118.691	29.584	89.107
Testomkostninger	55.000	0	55.000
Bivirkninger	4.105	0	4.105
Patientomkostninger	37.469	10.177	27.291
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 8. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC for børn (klinisk spørgsmål 2), DKK, diskonterede tal

	Larotrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	196.232	29.584	166.648
Testomkostninger	0	0	0
Bivirkninger	6.156	0	6.156
Patientomkostninger	59.451	10.177	49.274
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 9.

Tabel 9. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger (voksne)	Inkrementelle omkostninger (børn)
Resultatet af hovedanalysen	[redacted]	[redacted]
Kurver anvendt i Medicinrådets afrapportering vedr. entrectinib til NTRK-fusion-positiv kræft	[redacted]	[redacted]
PFS for larotrectinib:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
OS for larotrectinib:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Scenarie	Inkrementelle omkostninger (voksne)	Inkrementelle omkostninger (børn)
[redacted]	[redacted]	[redacted]
Ingen testomkostninger	[redacted]	[redacted]
Patientantal på 20 (10 voksne og 10 børn)	[redacted]	[redacted]
Patientantal på 40 (30 voksne og 10 børn)	[redacted]	[redacted]
NGS anvendes som test	[redacted]	[redacted]
2.000 patienter skal testes for at finde de 20 voksne patienter (70.000 DKK testomkostninger per patient)	[redacted]	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at larotrectinib vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Larotrectinib bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Larotrectinib bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Ansøgers estimat af patientantal og markedsandel

[redacted]

[redacted]

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse

Fagudvalget fremhæver, at der er betydelig usikkerhed ved estimering af patientantal, men estimerer, at der vil være ca. 20 nye patienter det første år (10 børn og 10 voksne), og derefter vil ca. 30 patienter om året (10 børn og 20 voksne) forventes at være kandidater til behandling med larotrectinib til den pågældende indikation. Fagudvalget forventer et markedsoptag på 100 % blandt disse patienter. Sekretariatet vælger derfor at justere patientantallet, som er præsenteret i Tabel 10, men præsenterer desuden en følsomhedsanalyse af patientantallet, da dette også har betydning for de inkrementelle testomkostninger.

Tabel 10. Medicinrådets estimat af antal nye patienter pr. år

		År 1	År 2	År 3	År 4	År 5
				Anbefales		
Larotrectinib	Voksne	10	20	20	20	20
	Børn	10	10	10	10	10
BSC	Voksne	10	0	0	0	0
	Børn	0	0	0	0	0
				Anbefales ikke		
Larotrectinib	Voksne	0	0	0	0	0
	Børn	0	0	0	0	0
BSC	Voksne	20	20	20	20	20
	Børn	10	10	10	10	10

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet er ændret til 20 (10 børn og 10 voksne) patienter i år 1 og 30 (10 børn og 20 voksne) patienter pr. år de efterfølgende år.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- 20 (10 børn og 10 voksne) patienter i år 1 og 30 (10 børn og 20 voksne) pr. år de efterfølgende år.

Medicinrådet estimerer, at anvendelse af larotrectinib hos voksne patienter vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5, mens det for børn vil resultere i budgetkonsekvenser på ca. [redacted] DKK. Resultatet er præsenteret i Tabel 11 og Tabel 12.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 28,9 DKK i år 5 for voksne og 12,3 mio. DKK for børn.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser for voksne (klinisk spørgsmål 1), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 12. Medicinrådets analyse af totale budgetkonsekvenser for børn (klinisk spørgsmål 2), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med larotrectinib er forbundet med inkrementelle omkostninger på hhv. [redacted] og [redacted] DKK for voksne og børn sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for larotrectinib. Der er dog i denne analyse betydelige usikkerheder, som medfører, at resultatet skal tolkes med forsigtighed. Disse usikkerheder er præsenteret nedenfor.

Ekstrapolerede kurver:
De ekstrapolerede kurver i denne analyse er særdeles usikre. Ansøger har ikke redegjort for den kliniske plausibilitet af de ekstrapolerede kurver for larotrectinib, men kun baseret valget af parametrisk funktion på det statistiske fit. Fagudvalget vurderer, at disse kurver er behæftet med meget stor usikkerhed, og den kliniske plausibilitet af disse kurver er tvivlsom. Fagudvalget vurderer, at nogle børn vil blive langtidsoverlevere, og

derfor vælger Medicinrådet at ekstrapolere med en parametrisk funktion, hvor de underliggende antagelser tilsiger, at nogle patienter vil blive langtidsoverlevere. Ved de ekstrapolerede kurver for voksne i behandling med larotrectinib vurderer fagudvalget, at ansøgers kurver kan være plausible, men fagudvalget vurderer dog, at ekstrapolering med den eksponentielle funktion i højere grad afspejler det forventelige forløb for patienterne, hvorfor Medicinrådet har valgt denne. For data vedr. BSC har ansøger anvendt data for doxorubicin for både børn og voksne, hvilket, fagudvalget vurderer, ikke er relevant i dansk klinisk praksis, men da det i sundhedsøkonomiske analyser er nødvendigt med kvantitative estimater, vælger Medicinrådet at acceptere de anvendte data for doxorubicin som proxy for BSC. Medicinrådet vælger dog at fjerne alle lægemiddelomkostninger vedr. doxorubicin, og derfor vil valget af ekstrapolering have mindre betydning på de totale omkostninger for BSC.

Alle disse ekstrapolerede kurver er meget tvivlsomme og bidrager med meget usikkerhed til modellen. Følsomhedsanalyserne illustrerer netop, at valget af parametrisk funktion har stor betydning for det endelige resultat. Afhængig af modelvalg varierer de inkrementelle omkostninger fra knap [redacted] DKK til knap [redacted] DKK per patient.

Test for NTRK-fusion:
Der er usikkerhed omkring den gennemsnitlige omkostning til test for NTRK-fusion. Fagudvalget vurderer, at mellem 1.500 og 2.000 patienter skal testes for at finde de 20 voksne patienter, som vil være kandidater til behandling med larotrectinib. I Medicinrådets hovedanalyse antages, at 1.500 patienter skal testes. Hvis 2.000 patienter i stedet skal testes, så vil de inkrementelle omkostninger stige med 10.000-15.000 DKK per patient. Det er ikke muligt for fagudvalget at give et mere præcist estimat, og der er derfor betydelig usikkerhed vedr. testomkostningerne. Derfor vælger Medicinrådet at anvende et konservativt estimat på 1.500 årlige test, hvilket giver en gennemsnitlig testomkostning på 55.000 DKK per patient, men følsomhedsanalysen vedr. test viser, at de inkrementelle omkostninger stiger med 15.000 DKK, hvis der skal foretages 2.000 test med IHC for at finde 20 patienter, hvorimod de inkrementelle omkostninger falder med 8.000 DKK, hvis det antages, at 1.500 patienter testes med IHC, men der identificeres 30 voksne.

Patientantal:
Der er usikkerhed vedr. det præcise antal patienter, der kandiderer til behandling med larotrectinib. Fagudvalget skønner, at mellem 10 og 40 patienter (voksne og børn) årligt er kandidater til behandlingen med larotrectinib i Danmark. Antallet af patienter er dog usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og dels er larotrectinib først indiceret, når øvrige muligheder for behandling er udtømte. Derfor skal et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer. I Medicinrådets hovedanalyse antages det, at 20 patienter (10 børn og 10 voksne) vil kandidere til behandling med larotrectinib i det første år, mens der i de efterfølgende år vil være 30 patienter (10 børn og 20 voksne), der kandiderer til behandling med larotrectinib. Usikkerheden ved patientantallet har betydning for budgetkonsekvenserne, men har også betydning for de gennemsnitlige testomkostninger.

BSC:
Der er i modellen ikke inkluderet lægemiddelomkostninger for patienter i behandling med BSC. Dette kan potentielt være en underestimering af omkostningerne ved behandling med BSC, da patienterne sandsynligvis vil modtage symptomlindrende behandling, og derved vil de inkrementelle omkostninger være overestimerede. Denne usikkerhed er dog svær at kvantificere.

8. Referencer

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	23. juni 2021	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers analyse bliver de inkrementelle omkostninger ca. [redacted] DKK for voksne og ca. [redacted] for børn i Medicinrådets hovedanalyse DKK. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 13 og Tabel 14.

Tabel 13. Resultatet af ansøgers analyse ved sammenligning med BSC for voksne (klinisk spørgsmål 1), DKK, diskonterede tal

	Larotrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	930.225	365.905	564.320
Testomkostninger	151.250	151.250	0
Bivirkninger	5.000	5.000	0
Patientomkostninger	123.065	46.570	76.495
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 14. Resultatet af ansøgers analyse ved sammenligning med BSC for børn (klinisk spørgsmål 2), DKK, diskonterede tal

	Larotrectinib	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	1.387.999	281.484	1.106.515
Testomkostninger	0	0	0
Bivirkninger	5.000	5.000	0
Patientomkostninger	246.608	46.570	200.038
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med de ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af larotrectinib hos voksne patienter vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5, mens det for børn vil resultere i budgetkonsekvenser på ca. [redacted] DKK.

Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 15 og Tabel 16.

Tabel 15. Ansøgers analyse af totale budgetkonsekvenser for voksne (klinisk spørgsmål 1), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 16. Ansøgers analyse af totale budgetkonsekvenser for børn (klinisk spørgsmål 2), mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	23.06.2021
Leverandør	Bayer
Lægemiddel	Larotrectinib (vitrakvi)
Ansøgt indikation	Behandling af NTRK-fusion positiv kræft.

Forhandlingsresultat

Amgros har opnået følgende pris på larotrectinib:

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Larotrectinib	100 mg	56 stk.	44.839,84	[redacted]	[redacted]
Larotrectinib	25 mg	56 stk.	11209,96	[redacted]	[redacted]
Larotrectinib oral opløsning	20 mg/ml	100 ml	16014,23	[redacted]	[redacted]

Der er indgået en kontrakt med start d. 24.06.2021 og vil gælde i 3 måneder.

[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi på nuværende tidspunkt ikke har opnået den bedste pris på larotrectinib. Denne vurdering baserer vi på følgende punkter:

- Leverandøren påpeger at data er markant bedre end den kliniske merværdi larotrectinib er blevet tildelt.

[redacted]

Konklusion

Det er Amgros vurdering at prisen på larotrectinib er for høj.

[redacted]

Relation til markedet

I marts 2021 valgte Medicinrådet ikke at anbefale entrectinib til samme indikation. Prisen for larotrectinib og entrectinib i rene lægemiddelpriser fremgår af tabellen nedenfor.

Lægemiddel	Styrke/dosis	Pakningsstørrelse	Antal pakninger	Pris for et års behandling SAIP (DKK)
Larotrectinib	100 mg	56 stk.	13,04	[redacted]
Entrectinib	200 mg	90 stk.	12,17	[redacted]

*Dette er den betinget pris på godkendelse af hele patientpopulationen.

Status fra andre lande

Sverige: NT-rådet valgte i november 2020 at anbefale larotrectinib til børn, men ikke voksne.[1]

UK: NICE valgte i maj 2020 at anbefale larotrectinib som mulig standardbehandling.[2]

Norge: Under behandling. Delt op i 2 indikationer, hhv. behandling hos børn under 12 år[3], og behandling af patienter over 12 år[4].

[1] Vitrakvi (larotrektinib) vid solida tumörer (janusinfo.se)
[2] Larotrectinib for treating NTRK fusion-positive solid tumours (nice.org.uk)
[3] Larotrectinib (Vitrakvi) (nyemetoder.no)
[4] Larotrectinib (Vitrakvi) - Indikasjon II (nyemetoder.no)

Fra: Annegret Trinczek <annegret.trinczek@bayer.com>
Sendt: 25. maj 2021 20:28
Til: Hans Christian Cederberg Helms <HCE@medicinraadet.dk>
Cc: Christian Graves Beck <CGB@medicinraadet.dk>; Dorte Glintborg <DGL@medicinraadet.dk>
Emne: RE: Høring over udkast til vurdering af lægemidlets værdi og sundhedsøkonomisk afrapportering for larotrectinib til NTRK-fusion-positiv kræft

Hej Hans,

Tack för samtalet idag! Vi vill tacka för en god rapport och värdering av Vitrakvi. Vi har inga kommentarer eller tillägg.
Vi ser nu över sekretessen markeringar.

Med vänliga hälsningar,

Annegret Trinczek
Market Access Lead Scandinavia & Health Economist
////////////////////

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Medicinrådet

Medicinrådets vurdering vedrørende larotrectinib til behandling af NTRK-fusion-positiv kræft

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	26. maj 2021
Dokumentnummer	116305
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. maj 2021

1. Medicinrådets konklusion

Medicinrådet finder, at den samlede værdi af larotrectinib overfor placebo til behandling af voksne og børn med NTRK-fusion-positiv kræft ikke kan kategoriseres. Vurderingen er baseret på enkeltarmede studier med en lille patientgruppe med forskellige kræftformer og deraf forskellige prognoser, der sammenstilles med observationelle data for patienter med NTRK-fusion-positiv kræft.

Medicinrådet vurderer, at datagrundlaget, om end meget usikkert, indikerer, at larotrectinib er en effektiv behandlingsmulighed for både voksne og børn, der ikke har andre tilfredsstillende behandlingsmuligheder.

Medicinrådet finder, at effekten er mere udtalt i børn end i voksne, hvilket særligt kommer til udtryk i effekten på overlevelsen.

Evidensens kvalitet er meget lav. Medicinrådet vurderer, at sjældenheden af NTRK-fusion og larotrectinibs vævsagnostiske indikation gør det vanskeligt at foretage en nøjagtig vurdering af larotrectinibs kliniske værdi.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

AE:	Uønsket hændelse (*adverse event*)
ARR:	Absolut risikoreduktion
BSC:	*Best supportive care*
CHMP:	*Committee for Medicinal Products for Human Use*
CI:	Konfidensinterval (*confidence interval*)
CNS:	Centralnervesystemet
CR:	Komplet respons (*complete response)*
CTCAE:	*Common Terminology Criteria for Adverse Events*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European public assessment report*
ESMO:	*European Society for Medical Oncology*
FISH:	*Flourescence in situ hydridization*
GMI:	*Growth Modulation Index*
GRADE:	System til vurdering af evidens *(Grading of Recommendations Assessment, Development and Evaluation)*
HR:	*Hazard ratio*
IHC:	*Immunohistochemistry*
ITT:	*Intention-to-treat*
MCBS:	*Magnitude of Clinical Benefit Scale*
MKRF:	Mindste klinisk relevante forskel
NGS:	*Next Generation Sequencing*
OR:	Odds ratio (*odds ratio*)
ORR:	Objektiv responsrate (o*bjective response rate*)
OS:	Overlevelse (*overall survival)*
pCR:	Patologisk komplet respons (*pathological complete respons*)
PFS:	Progressionsfri overlevelse (*progression-free survival)*
PR	Partielt respons (*partial response*)
R0:	Komplet resektion
RR:	Relativ risiko
RECIST:	*Response Evaluation Criteria in Solid Tumors*

3. Introduktion

Formålet med Medicinrådets vurdering af larotrectinib til behandling af kræft med NTRK-fusion er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling. Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Bayer. Medicinrådet modtog ansøgningen den 19. marts 2021.

De kliniske spørgsmål er:
1. Hvad er den kliniske merværdi af larotrectinib til behandling af voksne med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

2. Hvad er den kliniske merværdi af larotrectinib til behandling af børn med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

3.1 NTRK-fusion-positiv kræft

En solid tumor er en unormal vævsmasse (svulst). Solide tumorer kan være benigne (ikke kræft) eller maligne (kræft), hvor sidstnævnte kan gennemtrænge væv eller sprede sig til andre dele af kroppen. Kræft inddeles i forskellige typer, afhængig af hvilken celletype kræften udgår fra. Solidt voksende kræfttyper kan overordnet inddeles i f.eks. sarkomer (bløddels- og knoglekræft), karcinomer (epitel deriverede kræftformer), neurogen deriverede tumorer og melanomer (modermærkekræft). For hver af disse overordnede kræfttyper findes talrige undertyper, baseret på hvilken celletype de udgår fra, hvilke histopatologiske og eventuelle molekylærbiologiske forandringer der kendetegner kræften [1,2]. De forskellige kræftformer rammer forskelligt i befolknings- og aldersgrupper og kræver forskellig diagnostik og behandling.

Forekomsten af kræft i Danmark er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000, lidt flere mænd end kvinder. Den største andel af nye kræfttilfælde er i den ældre del af befolkningen. 2/3 af alle nye kræfttilfælde er hos personer over 60 år. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [3].

Selvom kræft er sjældent hos børn (under 18 år), er det den næst hyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 200 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [3]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [4].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, NTRK1, NTRK2 og NTRK3, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, koder for Trk-fusionsproteiner, som kan medføre ukontrolleret Trk-signalering og

dermed tumorvækst [5,6]. NTRK-fusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-fusioner. NTRK-fusioners hyppighed i forskellige kræftformer er angivet i tabellen nedenfor. Dette skal dog tages med forbehold for de ovennævnte forskelle.

Tabel 3-1. Oversigt over frekvens for NTRK-fusion ved forskellige kræftformer

Kræftform	Frekvens for NTRK-fusion
Infantil fibrosarkom	Omkring 100 % [7,8]
Sekretorisk karcinom i både spytkirtel og bryst	Omkring 100 % [7,8]
Kræfttyper i luftveje, fordøjelseskanal, bryst og hjerne	< 5 % [7,8]
Lungekræft, kolorektalkræft, modermærkekræft og brystkræft	0,1-1 % [9]

3.2 Larotrectinib

Trk-fusionsproteiner virker som 'onkogene drivere', der fremmer celledeling og overlevelse af tumorceller. Larotrectinib er en TRK-hæmmer, som hindrer neurotrophin-Trk-interaktion og dermed Trk-aktivering. Dette fører til celledød og hæmning af tumorer, som overudtrykker Trk [8,10,11].

Patienter kan behandles med larotrectinib, hvis de har en NTRK-fusion i en tumorprøve. Der testes i dag ikke rutinemæssigt for NTRK-fusion i tumorprøver, og der er ingen klinisk validerede tests eller '*companion diagnostics*' tilgængelige til at udføre testen. Man kan både anvende *next-generation sequencing* (NGS), immunhistokemi (IHC) og *fluorescence in situ hydridization* (FISH) for at påvise fusioner (se afsnit 6.4).

Larotrectinib er som enkeltstofbehandling indiceret til behandling af voksne og pædiatriske patienter med solide tumorer, der udtrykker en NTRK-genfusion. Derudover skal følgende være opfyldt:

- Sygdommen er lokalt avanceret, metastatisk, eller kirurgisk resektion vil sandsynligvis resultere i svær morbiditet.
- Der er ikke nogen andre tilfredsstillende behandlingsmuligheder.

De anbefalede doser af larotrectinib for voksne og børn med et kropsareal ≥ 1,0 m^2 er 100 mg oralt to gange dagligt. Til børn med et kropsareal < 1,0 m^2: 100 mg/m^2 oralt to gange dagligt (maksimalt 100 mg pr. dosis). Startdosis bør reduceres med 50 % hos patienter med moderat eller svær nedsat leverfunktion. Der kan ved bivirkninger foretages op til tre dosisreduktioner af 25 mg pr. dosis pr. reduktion. Behandlingen fortsættes indtil sygdomsprogression, uacceptabel toksicitet eller opnåelse af komplet

patologisk respons, som betyder, at patienten har fået bortopereret resttumor og derefter fået påvist fravær af sygdom ved en histologisk undersøgelse af det bortopererede væv.

Larotrectinib fik betinget markedsføringstilladelse af EMA den 19. september 2019. Ansøger skal indlevere data fra opfølgningsstudier i 2024, hvor den tumoragnostiske effekt yderligere dokumenteres med data fra flere patienter fra de igangværende studier, og udviklingen af sekundær resistens undersøges. Ydermere skal ansøger inden 2027 indlevere yderligere data for sikkerheden i børn, særligt med henblik på at undersøge risikoen for forstyrrelser i udviklingen af centralnervesystemets funktioner.

Estimat for antal patienter i Danmark
Antallet af patienter, der årligt er kandidater til behandling med larotrectinib i Danmark, er usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og derudover er larotrectinib først indiceret, når øvrige muligheder for behandling er udtømte. Derfor skal et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer.

En af forudsætningerne for behandling med larotrectinib er, at alle øvrige behandlingsmuligheder er udtømte. I denne sammenhæng henviser fagudvalget til gældende nationale retningslinjer og Medicinrådets behandlingsvejledninger inden for de forskellige relevante kræftområder.

Fagudvalget skønner, at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft og at ca. 1/3 af disse vil udtømme øvrige behandlingsmuligheder, men stadig være i tilstrækkelig almen tilstand til at modtage yderligere behandling. Det er således blandt disse ca. 3.000 patienter, at man skal identificere de patienter, som kan være kandidater til behandling med larotrectinib.

Fagudvalget tager i sit skøn højde for, at der vil være ganske få patienter med meget sjældne kræftformer, hvor NTRK-fusionen er hyppig (f.eks. infantil fibrosarkom) samt mange patienter med hyppigere kræfttyper (f.eks. tyk- og endetarmskræft, lungekræft og modermærkekræft), hvoraf kun ganske få (ca. 0,3 %) vil have en NTRK-fusion. Derudover skønner fagudvalget, at der blandt de 1.400 årlige tilfælde af hjernetumorer i Danmark [4] vil være maksimalt 10 patienter, som kan være kandidater til behandlingen. Fagudvalget skønner således samlet, at mellem 10 og 40 patienter (voksne og børn) årligt er kandidater til behandlingen i Danmark

Fagudvalget understreger, at der ikke foreligger tilstrækkelige data til at foretage en valid vurdering af antallet af patienter, hvorfor ovenstående skøn er forbundet med væsentlig usikkerhed. Estimatet afhænger tilmed i vid udstrækning af, hvordan screening efter NTRK-fusion implementeres, samt hvordan indikationen fortolkes, særligt udsagnet vedr. at øvrige behandlingsmuligheder skal være udtømte.

Fase 1-enheden på Rigshospitalet deltager i klinisk afprøvning af larotrectinib. Fagudvalget oplyser kendskab til tre danske patienter med NTRK-fusion-positiv kræft, som siden forsøgsstart i 2016 har modtaget behandling med larotrectinib.

3.3 Nuværende behandling

Hovedparten af patienter med kræft modtager standardbehandling, som primært afhænger af, hvilket væv kræften er opstået i, samt hvor udbredt kræften er. For en række kræfttyper er operation med henblik på helbredelse oftest førstevalg. Når kirurgisk behandling ikke er mulig eller ikke er tilstrækkelig, tilbydes patienterne enten strålebehandling og/eller medicinsk behandling (kemoterapi, targeteret behandling eller immunterapi).

Den valgte medicinske behandling afhænger af mange faktorer, herunder kræfttype, hvor udbredt sygdommen er, samt om kræfttypen eventuelt udtrykker særlige molekylærgenetiske forandringer, hvortil der er udviklet specifikke (targeterede) lægemidler. Herudover skal patienterne være i tilstrækkelig almen tilstand til at kunne tåle yderligere behandling. I studier måles almen tilstand ofte med ECOG-performance status [12].

For flere pædiatriske kræftformer er kemoterapi ofte førstevalg. For en lille andel af patienterne med meget sjældne kræftformer findes der ingen etableret standardbehandling. Derudover er der patienter med hyppigere kræftformer, som i løbet af deres behandlingsforløb udtømmer alle standardbehandlingsmuligheder. Disse patienter kan indgå i forsøg med eksperimentel behandling eller få tilbudt lindrende behandling (*best supportive care* (BSC)).

I modsætning til den traditionelle fremgangsmåde for kræftbehandling, kendetegnet ved i vid udstrækning at være histologi (vævstype)-afhængig, er larotrectinib ikke indiceret til én bestemt kræfttype, men til alle tilfælde af solide tumorer med NTRK-fusion (ofte benævnt som 'vævs-/tumor-agnostisk'). Af denne årsag, og fordi larotrectinib er indiceret, når øvrige muligheder for behandling er udtømte, findes der ikke standardbehandling for de patienter, som kandiderer til behandling med larotrectinib.

4. Metode

Medicinrådets protokol for vurdering vedrørende larotrectinib beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

Klinisk spørgsmål 1 er:

- Hvad er den kliniske merværdi af larotrectinib til behandling af voksne med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Studier af larotrectinib
Ansøger har søgt litteratur med søgestrengen fra protokollen og har udvalgt tre fuldtekstartikler, der beskriver larotrectinibs effekt og sikkerhed til behandling af NTRK-fusion-positiv kræft. Ansøger har desuden tilføjet en nylig publikation. De i alt fire artikler analyserer alle data fra de samme tre kliniske studier (SCOUT LOXO-TRK-15003, LOXO-TRK-14001 og NAVIGATE LOXO-TRK-15002. Se studiekarakteristika i bilag 1).

De to artikler af Laetsch og DuBois rapporterer en analyse af data specifikt for pædiatriske patienter fra SCOUT LOXO-TRK-15003. Herudover har ansøger anvendt data fra EPAR og produktresumé. Tidspunkt for data cut-off varierer i de forskellige publikationer, hvilket har betydning for både den mediane opfølgningstid og det totale patientantal, da både SCOUT og NAVIGATE stadig rekrutterer patienter.

Tabel 5-1. Oversigt over anvendt litteratur

Reference	Studier (NCT-nummer)	Beskrivelse	Data cut-off	Antal patienter
Drilon et al. 2018 [13]	LOXO-TRK-14001 (NCT02122913). SCOUT LOXO-TRK-15003 (NCT02637687). NAVIGATE LOXO-TRK-15002 (NCT02576431)	Børn (kun i SCOUT og NAVIGATE) og voksne (alle tre studier). I effektpopulationerne indgik kun patienter med påvist NTRK-fusion og minimum 6 måneders opfølgningstid. De samme patienter med længere opfølgningstid indgår i Hong et al. 2020 (se nedenfor).	Februar 2017	55

Reference	Studier (NCT-nummer)	Beskrivelse	Data cut-off	Antal patienter
Laetsch et al. 2018 [14]	SCOUT LOXO-TRK-15003 (NCT-02637687)	Børn med og uden NTRK-fusion. Patienterne fra dette studie med NTRK-fusion indgår også i Hong et al. 2020 (se nedenfor).	Februar 2017	24
DuBois et al. 2018 [15]	SCOUT LOXO-TRK-15003 (NCT-02637687)	Børn med infantilt fibrosarkom og påvist NTRK-fusion. De samme patienter indgår i Hong et al. 2020 (se nedenfor).	Februar 2017	5
EPAR [11]	LOXO-TRK-14001 (NCT-02122913) SCOUT LOXO-TRK-15003 (NCT-02637687) NAVIGATE LOXO-TRK-15002 (NCT-02576431)	Samme patienter som i Drilon et al. 2018 med længere opfølgningstid samt yderligere rekrutterede patienter fra SCOUT og NAVIGATE.	Juli 2018	102
Hong et al. 2020 [16]	LOXO-TRK-14001 (NCT-02122913) SCOUT LOXO-TRK-15003 (NCT-02637687) NAVIGATE LOXO-TRK-15002 (NCT-02576431)	Samlet analyse af larotrectinibs sikkerhed og effekt i børn og voksne med påvist NRKT-fusion. Længere opfølgningstid samt yderligere rekrutterede patienter fra SCOUT og NAVIGATE. Bivirkningsdata fra patienter uden NTRK-fusion er inkluderet.	Februar 2019	153 (260 for bivirkninger)
EMA produktresumé [17]	LOXO-TRK-14001 (NCT-02122913) SCOUT LOXO-TRK-15003 (NCT-02637687) NAVIGATE LOXO-TRK-15002 (NCT-02576431)	Objektive responsrater og responsvarighed på enkelttumorniveau, inklusive CNS-tumorer.	Juni 2019	188*

* Populationen indeholder 24 ud af de 188 patienter med primær CNS-tumor, som ikke er medtaget i de samlede effektestimater. Data for disse patienter er opgjort separat (se afsnit 6.1).

Ansøger referer til flere forskellige datasæt i ansøgningen (Tabel 5-2). Det første datasæt, 'PAS', er de samme 55 patienter, som indgik i Drilon et al. 2018, men ansøger har indsendt 'data-on file' for de samme patienter med en opfølgningstid, der er 2,4 år længere. Det andet datasæt 'ePAS' inkluderer yderligere patienter og indeholder ved seneste cut-off data fra i alt 164 patienter (samme data cut-off og patientantal, som er publiceret i EMAs produktresumé). Dette datasæt er inddelt i tre forskellige datasæt med forskellige opfølgningstider. Det seneste tilgængelige datasæt 'ePAS4' har dataopfølgning frem til juli 2019, og det er dette datasæt sammen med 'PAS'-datasættet, som den sundhedsvidenskabelig ansøgning baserer sig på.

I nedenstående skema ses en oversigt over datasættene, som de er navngivet i ansøgningen:

Tabel 5-2. Oversigt over datasæt

Datasæt	Dato for cut-off	Antal patienter i alt	Antal patienter < 18 år	Antal patienter ≥ 18 år	Publiceret
PAS	Juli 2019	55	12	43	(Drilon et al. 2018 [13])*
ePAS2	Juli 2018	102	34	68	EPAR 2019
ePAS3	Februar 2019	153** (159)	52	107	Hong et al., 2020 [16]
ePAS4	Juli 2019	164 (188***)	55	109	EMAs produktresumé [17]

*Drilon et al. 2018 [13] afrapporterer data for disse 55 patienter men med kortere opfølgning (cut-off februar 2017). ** Der indgår 159 patienter, hvorfra 153 er evaluerbare. *** Dette datasæt inkluderer også 24 patienter med primære CNS-tumorer. Data for disse patienter er opgjort separat (se afsnit 6.1).

I den sundhedsøkonomiske ansøgning har ansøger anvendt et senere data cut-off (ePAS5), som ikke er publiceret, og som ikke er tilgængeligt i den kliniske ansøgning. Datasættet indeholder kaplan meier plots for PFS og OS, men er ikke tilstrækkeligt beskrevet til at det kan lægges til grund for den kliniske vurdering.

ePAS4-datasættet anvendes til besvarelse af de kliniske spørgsmål, da dette er det komplette datasæt, der indeholder størst muligt patientantal med længst mulig opfølgningstid. Udover data for objektiv responsrate (publiceret i EMAs produktresumé) er alle data i ePAS4 angivet af ansøger som 'data on file'. Efterfølgende er disse data publiceret af Tandvårds- och Läkemedelsförmånsverket i deres beslutningsgrundlag for anbefalingen af larotrectinib i Sverige [18], hvorved de ikke betragtes som upublicerede data.

Baselinekarakteristika for ePAS4-datasættet er opsummeret nedenfor.

Tabel 5-3. Demografi og baselinekarakteristika for ePAS4-population ved data cut-off, juli 2019

Hovedkategori	Underkategori		Larotrectinib-effektpopulation (ePAS4) n = 164 (Data cut-off juli 2019)
Alder	Medianalder, år (rækkevidde)	Alle	42 (0,05-84)
		Voksne	56 (19-84)
		Børn	1,2 (0,05-14)
Køn, n (%)	Kvinde		85 (52 %)
Børn, n (%)			55 (34 %)
Eastern Cooperative Oncology Group - performance score, n (%)	0		79 (49 %)
	1		62 (38 %)
	≥2		23 (14 %)
Opfølgningstid	Median		14,5 måneder
Overordnet tumorhistologi, n (%)	Sarkom		36 (22 %)
	Ikke-småcellet lungekræft		13 (7,9 %)
	Spytkirtelkræft		21 (13 %)
	Skjoldbruskkirtelkræft		27 (16 %)
	Kolorektalkræft		8 (4,9 %)
	Brystkræft		5 (3,0 %)
	Infantil fibrosarkom		32 (20 %)
	Bugspytkirtelkræft		2 (1,2 %)
	Melanom		7 (4,3 %)
	Gastrointestinal stromal tumor		4 (2,4 %)
	Kolangiokarcinom		2 (1,2 %)
	Knoglesarkom		2 (1,2 %)
	Andre		5 (3,0 %)

Hovedkategori	Underkategori	Larotrectinib-effektpopulation (ePAS4) n = 164 (Data cut-off juli 2019)
Antal tidligere systemiske behandlingslinjer, n (%)	0	36 (22 %)
	1	50 (30 %)
	≥ 2	78 (48 %)
Mediantid siden diagnose, måneder		25,2
Metastaser ved studiestart, n (%)	Fjernmetastase generelt	136 (83 %)
	Hjerne	18 (11 %)

De hyppigste kræftformer, fraset primære CNS-tumorer, er sarkom, infantilt fibrosarkom, skjoldbruskkirtelkræft, spytkirtelkræft og ikke-småcellet lungekræft (n = 13-36). De øvrige kræftformer er hver repræsenteret med mindre end 10 patienter.

Data vedr. patienter med primære CNS-tumorer
Fagudvalget bemærker, at ansøger har opgjort data fra patienter med primære CNS-tumorer separat. Sekretariatet har i korrespondance med ansøger gjort opmærksom på, at denne opdeling ikke er i overensstemmelse med protokollen. Det angives i ansøgningen, at det jf. ansøgers opfattelse ikke er metodologisk forsvarligt at opgøre effektdata samlet, med henvisning til at primære CNS-tumorer er vurderet ud fra RANO-kriterier, mens øvrige vurderinger er foretaget på baggrund af RECIST-kriterierne. Fagudvalget bemærker, at dette argument ikke gør sig gældende for samlet overlevelse og livskvalitet, og at data fra patienter med CNS-tumorer er inkluderet i sikkerhedsdatasættet.

Ansøger har indsendt sparsomme data vedr. baselinekarakteristika for patienter med primære CNS-tumorer. De 24 patienter fra ePAS4-datasættet havde en gennemsnitlig alder på 8 år (spænd: 1,3-79 år), 83 % var under 18 år, og 54 % var kvinder. Alle patienter havde modtaget tidligere behandling for deres kræftsygdom (kirurgi, strålebehandling og/eller systemisk behandling).

Fagudvalget har forholdt sig til de separate data for patienter med primære CNS-tumorer, i et afsnit under 'andre overvejelser', ud fra samme effektmål, som protokollens to kliniske spørgsmål specificerer.

Studier af placebo eller anden systemisk behandling hos lignende patientgrupper
Studierne af larotrectinib er alle non-komparative, og ansøger har derfor, jf. protokollen, søgt efter studier, der kan anvendes til en indirekte sammenligning af larotrectinib med placebo. Ansøger har ikke fundet egnede studier. Derfor har ansøger i stedet fundet et

studie af 'anden systemisk behandling' (Judson et. al [19]) samt konstrueret en kontrolarm fra patienter, der har modtaget larotrectinib men ikke udvist objektivt respons (proxykontrol). Derudover har Medicinrådet tilføjet Rosen et al. [20], der indgik i Medicinrådets vurdering af NTRK-hæmmeren, entrectinib [21].

Tabel 5-4. Oversigt over mulige sammenligningsgrundlag

Reference	Studiedesign	Beskrivelse	NTRK-fusion	Placebo-arm	Antal patienter
Proxykontrol – 'Data on file' fra de kliniske studier af larotrectinib	Prospektivt, enkeltarm	Patienterne fra larotrectinib-studierne, der modtog larotrectinib, men ikke opnåede objektivt respons.	Ja	Nej	30
Judson et al. [19]	Prospektivt, RCT	Doxorubicin overfor doxorubicin plus ifosamid til førstelinje-behandling af lokal avanceret eller metastatisk bløddelssarkom.	Nej	Nej	455 (228 i doxorubicin-armen)
Rosen et al. [20]	Retrospektivt	Patienter med NTRK-fusion, som modtog anden systemisk behandling.	Ja	Nej	76

'Proxykontrollen' omfatter de 30 af i alt 164 patienter fra SCOUT, LOXO og NAVIGATE, som modtog larotrectinib uden at opnå objektivt respons (patienter med stabil eller 'progressiv sygdom', jf. RECIST-kriterier).

Baselinekarakteristika for proxy-kontrolgruppen svarer til den samlede studiepopulation (ePAS4-datasæt). Dog er der væsentligt færre pædiatriske patienter i proxy-kontrol-gruppen (10 %) end i det samlede datasæt (34,2 %). Sammenligningen mellem denne proxykontrolgruppe og hele patientgruppen, som modtog larotrectinib, vil uvægerligt resultere i væsentlige effektforskelle 'by-design', særligt for effektmålet ORR og i mindre grad PFS samt øvrige effektmål. Af disse årsager vurderer fagudvalget, at proxy-kontrollen ikke er relevant som supplerende sammenligningsgrundlag.

Judson et al. 2014 [19] rapporterer data fra et fase III, dobbeltblindet randomiseret klinisk studie, som undersøger doxorubicin mod doxorubicin kombineret med ifosfamid til førstelinjebehandling af voksne patienter med bløddelssarkom. Ansøger argumenterer for, at doxorubicin-armen kan være et relevant sammenligningsgrundlag for

larotrectinib, da bløddelssarkom er den hyppigste tumortype i datasættet for larotrectinib.

Fagudvalget bemærker, at der er væsentlige forskelle på patientpopulationerne i studiet af Judson et al. 2014 overfor ePAS4-datasættet vedr. larotrectinib:

- I studiet af Judson et al. 2014 indgår der udelukkende patienter med bløddelssarkom, hvorimod denne patientgruppe udgør under halvdelen af populationen behandlet med larotrectinib. Doxorubicin vil ikke være en relevant behandlingsmulighed for en væsentlig andel af de patienter, som indgår i studierne af larotrectinib. Bløddelssarkom betragtes desuden som en forholdsvis behandlingsrefraktær kræftform, hvilket kan medføre en skæv sammenligning til fordel for larotrectinib.
- I studiet af Judson et al. 2014 indgår der udelukkende voksne patienter ≥ 18 år, hvorimod ca. 1/3 af patienterne i datasættet for larotrectinib er < 18 år.
- I studiet af Judson et al. 2014 fremgår det, at doxorubicin gives som førstelinjebehandling. I datasættet for larotrectinib har 78 % af patienterne modtaget én eller flere tidligere systemiske behandlinger forud for larotrectinib.
- Patienterne i studiet af Judson et al. 2014 har ukendt NTRK-status.

Fagudvalget vurderer derfor, at studiet har meget lidt relevans som sammenligningsgrundlag. Fagudvalget vil dog i visse tilfælde inddrage studiet som supplerende information, i mangel af bedre. Dette datasæt benævnes 'doxorubicin-kontrol'.

Rosen et al. er et retrospektivt studie fra 2020, som rapporterer data for OS, PFS og ORR for 76 patienter med NTRK-fusion på tværs af en række kræfttyper. Heraf udviklede 51 fremskreden/metastatisk sygdom i observationsperioden på 37,2 måneder, og 35 patienter modtog kemoterapibehandling for deres fremskredne sygdom[20].

Fagudvalget vurderer, at det er det største observationelle datasæt, der findes for patienter med kræft med NTRK-fusion, og at alder og fordelingen af kræfttyper i nogen grad svarer til de patienter, der indgår i studierne af entrectinib. Studiet giver information om effekten af andre typer af systemisk behandling hos en patientgruppe tilsvarende larotrectinib-effektpopulationen men giver ingen information omkring effekten af placebo. Studiet indeholder ingen data for uønskede hændelser og livskvalitet. Populationskarakteristika for Rosen et al. fremgår nedenfor.

Tabel 5-5. Patientdemografi for Rosen et al. 2020 [20]

Kategori	*n* (%)
Totalt antal patienter	76*
Median alder, år (spænd)	52 (0-78)
Antal patienter < 18 år[1]	10 (13,2)

Kategori	*n* (%)
Antal kvinder	47 (61,8)
Kræfttype	
Spytkirtelkræft	12 (15,8)
Skjoldbruskkirtelkræft	10 (13,2)
Sarkom	9 (11,8)
Kolorektalkræft	8 (10,5)
Lungekræft	6 (7,9)
Melanom	5 (6,6)
Glioblastoma multiforme	4 (5,3)
Bugspytkirtelkræft	4 (5,3)
Andre	18 (23,7)
Kræftstadie på diagnosetidspunkt	
Lokaliseret (I-III), n (%)	34 (58,6)
Metastatisk (IV), n (%)	24 (41,4)
Tidligere behandling	
Antal behandlingslinjer	Ikke angivet
Kirurgi, n (%)	65 (87,8) (n = 74)
Strålebehandling, n (%)	33 (47,1) (n = 70)
Systemisk behandling, n (%)	57 (75)
Kræftstadie på diagnosetidspunkt	
Lokaliseret (I-III), n (%)	34 (58,6)
Metastatisk (IV), n (%)	24 (41,4)

*Med mindre andet angives. [1] NB: ekstraheret på baggrund af offentligt tilgængeligt rådata fra studiet (tilgængeligt her).

Studiepopulationen afviger fra larotrectinib-effektpopulationen på flere parametre.

- 41 % af patienterne havde metastatisk kræft ved diagnosetidspunktet. I larotrectinibstudiet havde 83 % af patienterne fjernmetastaser ved studiestart.
- Studiet estimerer OS-rater og median OS med udgangspunkt i tidspunktet for den oprindelige diagnose (uanset stadie), hvorfor disse estimater er usammenlignelige med tilsvarende resultater fra studierne af larotrectinib.
- 45 % af patienterne modtager på et tidspunkt i forløbet behandling med en TRK-hæmmer, hvilket påvirker effektestimaterne. Estimaterne for ORR er dog opgivet som bedste ORR efter kemoterapi på tværs af behandlingslinjer, hvorved TRK-hæmmere ikke indgår i dette.
- Fire ud af 76 patienter har primære CNS-tumorer (glioblastoma multiforme). I larotrectinibpopulationen indgår 24 patienter med primære CNS-tumorer, men disse indgår ikke i de samlede effektanalyser.

Fagudvalget vurderer, at studiet af Rosen et al. kan bidrage med information om effektmålene ORR og PFS for patienter med NTRK-fusion-positiv kræft som helhed. Studiet rapporterer dog kun resultater af aktive behandlinger og kan således ikke bruges som en komparator for larotrectinib. Resultaterne for disse effektmål kan dog anvendes til at sætte effekterne for larotrectinib i perspektiv i forhold til, hvad der kan forventes ved andre systemiske behandlinger af NTRK-fusion-positiv kræft.

Growth modulation index
Ansøger har indsendt en analyse, som sammenligner hver enkelt patients 'tid til næste behandling' ved den forudgående behandling med PFS/'tid til næste behandling' for larotrectinib (intrapatientanalyse/growth modulation index (GMI)). Analysen er tidligere præsenteret som poster på ESMO kongressen 2020 [22], og data er publiceret af Tandvårds- och Läkemedelsförmånsverket i deres beslutningsgrundlag for anbefalingen af larotrectinib i Sverige [18]. Der er ikke indsendt kvantitative data, om hvilke lægemidler patienterne blev behandlet med forud for larotrectinib. Det er dog værd at bemærke, at 22 % af patienterne ikke modtog nogen systemisk behandling inden larotrectinib, hvorfor den indsendte GMI-analyse kun indeholder data fra de resterende 78 % (n = 122). De indsendte data indeholder både en samlet analyse af hele populationen samt delanalyser af voksne (n = 83) og børn (n = 39).
Fagudvalget har kommenteret på data for 'growth modulation index' i et separat afsnit under 'andre overvejelser'.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Datagrundlaget for EMAs godkendelse samt den nærværende vurdering af larotrectinib er baseret på de tre ovennævnte igangværende studier. Ansøger har indsendt to forskellige bud på sammenligningsdata samt den ovennævnte GMI-analyse.

Det kliniske spørgsmål omfatter også patienter med primære CNS-tumorer. Ansøger har valgt at ekskludere patienter med primære CNS-tumorer i den samlede dataanalyse og opgør i stedet disse patienter som en selvstændig subgruppe. Effektestimaterne i afsnit 5.1.4 er derfor ikke dækkene for patienter med primære CNS-tumorer. Disse behandles i stedet isoleret under andre overvejelser (afsnit 6.1).

Fagudvalget vurderer, at ingen af de indsendte data tillader en statistisk sammenligning, der kan ligge til grund for en kategorisering af larotrectinibs værdi ud fra Medicinrådets metoder.

I gennemgangen af resultater vil de poolede data for larotrectinib ved det senest tilgængelige data cut-off (ePAS4-datasættet) blive sammenholdt med data fra studiet af Rosen et. al [20] og i visse tilfælde Judson et al. [19] (doxorubicin-kontrol), disse er udelukkende supplerende data. For uønskede hændelser lægger fagudvalget vægt på data fra larotrectinib-effektpopulationen, da disse må formodes at have modtaget en behandling, der er mere repræsentativ for, hvad patienterne vil modtage i klinisk praksis.

5.1.3 Evidensens kvalitet

Vurderingen er baseret på data fra enkeltarmede studier, der i mangel på studier af den valgte komparator (placebo) sammenholdes med studier af lignende patientgrupper, som modtager anden systemisk behandling. Der findes ikke velvaliderede værktøjer til at vurdere evidensens kvalitet for non-komparative studier. Der er derfor hverken udarbejdet en Risk of Bias-profil eller en GRADE-profil.

På baggrund af det indirekte sammenligningsgrundlag, vurderer Medicinrådet, at evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

Fagudvalget bemærker dog, at det på grund af sjældenheden af NTRK-fusion i det hele taget er vanskeligt at gennemføre randomiserede forsøg med tilstrækkeligt patientantal til at kunne foretage en retvisende vurdering af larotrectinibs kliniske værdi ved brug af Medicinrådets metoder.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår effektestimaterne for larotrectinib, 'doxorubicin-armen' og studiet af Rosen et al. 2020 [20]. Herudover fremgår de aggregerede kategorier samt den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1. Bemærk, at data, som tidligere nævnt, ikke inkluderer patienter, som har primære CNS-tumorer. De analyseres separat under andre overvejelser (afsnit 6.1).

Tabel 5-6. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Larotrectinib	Supplerende sammenligningsdata*		Aggregeret værdi for effektmålet
			Estimat [95 % CI]	Rosen et al. 2020 [20] (estimat [95 % CI])	Doxorubicin-kontrol (estimat [95 % CI])	
Overlevelse	Median OS i antal måneder (MKRF: 3 måneder)	Kritisk	Median for overlevelse er endnu ikke nået ved seneste data cut-off (44,4 måneder [36,5; IN])**	***	Ikke angivet	Kan ikke kategoriseres
	OS-rate ved 24 måneder (MKRF: 5 %)		76 % [66; 86]	Ikke angivet	28 % [22; 34]	
	Andel patienter med komplet patologisk respons (MKRF: 5 %)		Ingen dokumenterede ****	Ikke angivet	Ikke angivet	
Livskvalitet	Forskel i gennemsnitlig ændring i EORTC-QLQ-C30 (MKRF: 10 point)	Kritisk	Ændring præ vs. post-baseline: 5,63 point (n = 74)	Ikke angivet	Ikke angivet	Kan ikke kategoriseres
Objektiv responsrate	Samlet ORR for hele den voksne patientpopulation (MKRF: narrativ vurdering)	Vigtigt	71,6 % [62; 79]	62,5 % [40,6; 81,2] *****	14 %	Kan ikke kategoriseres

Effektmål	Målenhed (MKRF)	Vigtighed	Larotrectinib	Supplerende sammenligningsdata*		Aggregeret værdi for effektmålet
			Estimat [95 % CI]	Rosen et al. 2020 [20] (estimat [95 % CI])	Doxorubicin-kontrol (estimat [95 % CI])	
Progressionsfri overlevelse	Median PFS (MKRF: 3 måneder)	Vigtigt	25,8 måneder [15,2; IN]	9,1 måneder [4,8; 13,1]	4,6 måneder [2,9; 5,6]	Kan ikke kategoriseres
	PFS-rate ved 12 måneder (MKRF: 10 %-point)		62 % [52; 72]	37 % [24; 51]	Ca. 12 % (ikke rapporteret)	
Uønskede hændelser	Andel patienter med én eller flere uønskede hændelser grad 3-4 (MKRF: 5 %-point)	Vigtigt	44 %	Ikke angivet	Ikke relevant	Kan ikke kategoriseres
	Kvalitativ gennemgang af uønskede hændelser					

Konklusion

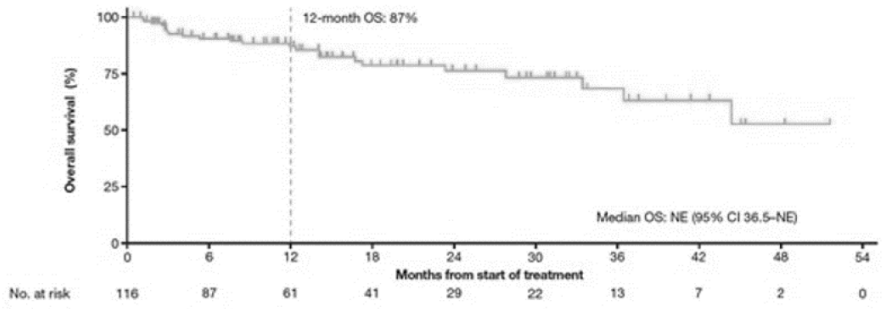
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget finder det sandsynligt, at larotrectinib er en effektiv behandling med acceptable bivirkninger til voksne med NTRK-fusion-positive kræftformer, der ikke har andre behandlingsmuligheder.
Kvalitet af den samlede evidens	Meget lav.

*Det supplerende data er præsenteret til orientering. Hverken data fra Rosen et al. 2020 [20] eller doxorubicin-studiet er tilstrækkeligt sammenlignelige med datasættet for larotrectinib til at kunne danne grundlag for en kategorisering af lægemidlets værdi. ** Estimatet er fra et tidligere cut-off (Hong et al. 2020) og er afledt af data fra n = 153 voksne og pædiatriske patienter ved en median opfølgningstid på 12,9 måneder. *** Data for samlet overlevelse fra Rosen et al. 2020 er usammenligneligt med data vedr. effekten af larotrectinib (se afsnit 5.1.1). **** Fagudvalget bemærker, at populationen ikke forventes at være kandidater til kurativt intenderet operation, hvorfor komplet patologisk respons ikke kan dokumenteres. ***** Bedste respons på kemoterapi på tværs af alle behandlingslinjer. CI = konfidensinterval. IN = ikke nået.

Overlevelse

Effektmålet overlevelse er kritisk for vurderingen af lægemidlets værdi for patienterne. Forbedret samlet overlevelse (OS) eller helbredelse med bedst mulig livskvalitet og mindst mulig toksicitet er det optimale mål for livsforlængende kræftbehandling. Overlevelse vurderes ved hjælp af komplet patologisk respons, som betyder, at patienten har fået bortopereret resttumor og derefter fået påvist fravær af sygdom ved en histologisk undersøgelse af det bortopererede væv.

Medianoverlevelsen for voksne er ikke nået ved det sidste data cut-off med en median opfølgningstid på 15,8 måneder. Et tidligere cut-off (Hong et al. 2020) viste dog en median OS på 44,4 måneder efter en median opfølgningstid på 13,9 måneder. Overlevelsesraten efter 24 måneder var 76 %. Der var ingen dokumenteret komplet patologisk respons i voksne. Fagudvalget bemærker, at populationen ikke forventes at være kandidater til kurativt intenderet operation, hvorfor komplet patologisk respons ikke kan dokumenteres.



Figur 5-1. Overlevelse for voksne patienter behandlet med larotrectinib. Data stammer fra hele voksenpopulationen fra ePAS4, inklusive 7 patienter med en opfølgningstid mindre end 6 måneder, der ellers ikke er medtaget i effektestimaterne. Kurven er publiceret som poster ved ASCO 2020 [23].

Der findes ikke et egnet sammenligningsgrundlag til at vurdere larotrectinibs effekt på OS. I doxorubicin-kontrollen var median-overlevelsen for voksne 12,8 måneder. Som tidligere beskrevet kan den ikke give et retvisende billede af den forventede OS for den samlede population, men data indikerer dog en samlet lav overlevelse ved førstelinje-standardbehandling af patienter med uhelbredeligt bløddelssarkom.

Der er ikke indsendt data vedr. overlevelse for de enkelte kræfttyper.

Samlet set forventes det, at restlevetiden er lav for voksne patienter, der kandiderer til larotrectinibbehandling. Derfor vurderer fagudvalget, at de observerede kliniske overlevelsesdata for larotrectinib indikerer en betydelig positiv effekt på restlevetiden for den samlede voksenpopulation.

Idet der ikke foreligger data, som tillader en sammenligning mellem larotrectinib og placebo, kan lægemidlets foreløbige værdi for overlevelse ikke kategoriseres.

Livskvalitet
Livskvalitet er et kritisk patientrelateret effektmål, da patienter, der responderer på larotrectinib, kan være kandidater til langvarig behandling. Livskvalitet er undersøgt vha. EORTC-QLQ-C30 og angivet som forskellen mellem gennemsnitsscoren fra den sidste tilgængelige undersøgelse versus den gennemsnitlige score før behandlingsstart. Data er kun medtaget fra patienter, der har besvaret skemaet før behandlingsstart og ved minimum én efterfølgende måling, hvorved gennemsnitsmålingerne bygger på 74 patienter. Værdierne før behandlingsstart og ved sidste måling var henholdsvis 64,5 ± 23,5 og 70,1 ± 19,5, hvilket giver en positiv ændring på 5,63 point. Ændringen er statistisk signifikant men mindre end den definerede MKRF på 10 point. Fagudvalget bemærker, at der mangler data fra ca. 1/3 af patienterne, hvilket kan resultere i bias ift. den intra-individuelle ændring i livskvalitet før versus efter behandling med larotrectinib.

Der er ikke indsendt data vedr. livskvalitet for de enkelte kræfttyper.

Da der udelukkende foreligger data fra single-arm-studier, kan larotrectinibs foreløbige værdi for livskvalitet ikke kategoriseres. Fagudvalget bemærker dog, at den samlede effekt på patientgruppen var statistisk signifikant og peger i positiv retning.

Objektiv responsrate
Som beskrevet i protokollen er effektmålet objektiv responsrate vigtig for vurderingen af lægemidlets værdi for patienterne. Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og afspejler interventionens umiddelbare antineoplastiske potentiale.

De voksne patienter havde en objektiv responsrate på 71,6 %, hvoraf 10,1 % var komplet respons, og 61,5 % var partielt respons.

I studiet af Rosen et. al opnåede gennemsnitlig 62,5 % et objektivt respons [20]. Dette var dog angivet som det bedste respons på tværs af behandlingslinjer og er derved ikke nødvendigvis repræsentativt for respons på en sidstelinjebehandling.

ORR for doxorubicinkontrolgruppen var 14 %, hvoraf 1 % var komplet respons, og 13 % var partielt respons.

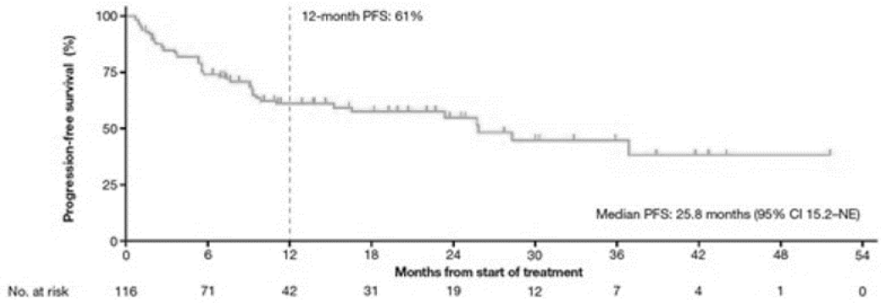
Fagudvalget efterspurgte en gennemgang af ORR per tumortype. Dette er ikke angivet specifikt for den voksne population men kun for den samlede population (voksne og børn). Derfor behandles dette ikke yderligere her, men ORR per tumortype i den samlede population kommenteres under 'andre overvejelser' (afsnit 6.3).

Samlet set vurderer fagudvalget, at ORR er høj på tværs af voksenpopulationen. Her tages højde for, at størstedelen af patienterne (ca. 80 %) tidligere har modtaget én eller flere systemiske behandlinger. Larotrectinibs værdi kan dog ikke kategoriseres pga. manglende komparativt data.

Progressionsfri overlevelse

Progressionsfri overlevelse bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. Fagudvalget vurderer, at det er vigtigt for patienterne ikke at have sygdomsprogression i længst mulig tid. Patienter med sygdomsprogression kan have generende symptomer, og den aktuelle patientgruppe har ingen efterfølgende behandlingsalternativer. Den mindste klinisk relevante forskel blev i protokollen fastsat til 3 måneder.

Median progressionsfri overlevelse for voksne patienter var 25,8 måneder [15,2; ikke nået], og 61 % [75 - 97 %] var progressionsfri efter 12 måneder.



Figur 5-2. Progressionsfri overlevelse for voksne patienter behandlet med larotrectinib. Data stammer fra hele den voksne patientpopulation fra ePAS4, inklusive 7 patienter med en opfølgningstid mindre end 6 måneder, der ellers ikke er medtaget i effektestimaterne. Kurven er publiceret som poster ved ASCO 2020 [23].

I studiet af Rosen et al. var median PFS 9,1 måneder [4,8; 13,1] og 37 % [24; 51] var progressionsfri efter 12 måneder [20]. Disse data stammer kun fra patienter med lokalfremskreden eller metastatisk sygdom og er derfor mere sammenlignelige, end det er tilfældet for data vedr. overlevelse. Dog repræsenterer PFS-data fra Rosen et al. en aktiv behandling i førstelinje, og det kan derfor ikke anvendes til at vurdere effekten af larotrectinib overfor placebo.

Doxorubicin-kontrollen viste endnu lavere PFS med en median på 4,6 måneder [2,9; 5,6] og ca. 12 % var progressionsfri efter 12 måneder.

Der er ikke indsendt data vedr. PFS for de enkelte kræfttyper.

Samlet set kan larotrectinibs foreløbige værdi for PFS ikke kategoriseres grundet manglende komparativt data. Fagudvalget vurderer, at PFS ved larotrectinibbehandling er lang. Den naive sammenstilling med patienterne i Rosen et al. viser en absolut forskel på ca. 16 måneder for median PFS og 24 %-point i PFS-raten ved 12 måneder, hvilket er væsentlig over den mindste klinisk relevante forskel. Derudover oplevede størstedelen af patienterne en væsentlig længere PFS ved larotrectinibbehandlingen end ved deres foregående systemiske behandling (se afsnit 6.2 om GMI), hvilket også taler for en betydelig effekt af larotrectinib på dette effektmål.

Uønskede hændelser

Fagudvalget efterspurgte i protokollen andelen af patienter, der oplevede minimum én uønsket hændelse af grad 3-4, og fastsatte den mindste klinisk relevante forskel til 5 %-point. En oversigt over de mest almindelige uønskede hændelser for voksne patienter ved larotrectinibbehandling er vist i tabellen nedenfor. Denne tabel inkluderer kun uønskede hændelser, der optræder i mere end 15 % af patienterne og er derfor ikke udtømmende.

Tabel 5-7. Oversigt over de mest almindelige uønskede hændelser for voksne behandlet med larotrectinib

Voksne patienter med NTRK-fusion-positiv kræft (n = 116)	Uønskede hændelser observeret under behandlingsforløb, n (%)			
	Grad 1-2	Grad 3	Grad 4	Total
Svimmelhed	44 (38)	2 (2)	0	46 (40)
Træthed	41 (35)	2 (2)	0	43 (37)
Forstoppelse	40 (34)	0	0	40 (34)
Øget alanin-aminotransferase	30 (26)	3 (3)	2 (2)	35 (30)
Hoste	33 (28)	1 (1)	0	34 (29)
Anæmi	21 (18)	12 (10)	0	33 (28)
Kvalme	31 (27)	1 (1)	0	32 (28)
Diarré	27 (23)	3 (3)	0	30 (26)
Øget aspartat-aminotransferase	26 (22)	2 (2)	1 (1)	29 (25)
Myalgi	28 (24)	1 (1)	0	29 (25)
Perifert ødem	29 (25)	0	0	29 (25)
Dyspnø	20 (17)	4 (3)	0	24 (21)
Ledsmerter	23 (20)	0	0	23 (20)
Hovedpine	22 (19)	0	0	22 (19)
Rygsmerter	19 (16)	2 (2)	0	21 (18)
Vægtøgning	17 (15)	3 (3)	0	20 (17)
Opkast	17 (15)	0	0	17 (15)

Data stammer fra hele den voksne patientpopulation fra ePAS4, inklusive 7 patienter med en opfølgningstid mindre end 6 måneder, der ellers ikke er medtaget i effektestimaterne. Tabellen stammer fra en poster præsenteret på ASCO 2020 [23].

Ansøger har også vedlagt en liste over samtlige uønskede hændelser i den voksne patientgruppe, der inkluderer alle voksne med NTRK-fusion-positiv kræft, der har modtaget minimum én dosis larotrectinib (n = 116).

De hyppigste uønskede hændelser hos voksne var svimmelhed, træthed og forstoppelse, mens de hyppigste grad 3-4 uønskede hændelser var anæmi (10 %), lymfocytopeni (7 %), sepsis (5 %) og øget alanin-aminotransferaseniveau (5 %). Samlet set oplevede 44 % af patienterne minimum én grad 3-4-uønsket hændelse, og disse var årsag til behandlingsstop for 7 %, mens 10 % blev håndteret ved hjælp af dosisreduktion. Fagudvalget bemærker, at resultater for andel af patienter med uønskede hændelser reflekterer akkumulation over en lang behandlingsperiode, hvilket er usædvanligt i en palliativ population.

Den kliniske værdi af larotrectinib ift. placebo kan ikke kategoriseres.

Fagudvalget vurderer, at larotrectinib fremstår relativt skånsomt overfor andre hyppigt anvendte tyrosinkinasehæmmere, hvilket er i overensstemmelse med fagudvalgets begrænsede kliniske erfaring med stoffet. Desuden vurderer fagudvalget, at patienterne generelt kan behandles for de grad 3-4-uønskede hændelser, som er forbundet med behandling med larotrectinib.

5.1.5 Fagudvalgets konklusion vedr. voksne

Den kliniske værdi af larotrectinib overfor placebo, til behandling af voksne med NTRK-genfusion-positiv kræft, hvor øvrige tilfredsstillende behandlingsmuligheder er udtømte, kan ikke kategoriseres. Dette skyldes mangel på et komparativt datagrundlag. Fagudvalget finder det sandsynligt at larotrectinib er en effektiv behandling med en acceptabel bivirkningsprofil. Dette er baseret på:

- OS-estimater, der indikerer lang restlevetid.
- Høje responsrater og lang PFS (også sammenholdt med anden systemisk behandling).
- Data for livskvalitet som indikerer, at patienterne ikke oplever en reduktion af livskvalitet under behandlingen men derimod en tendens til en øget livskvalitet.
- Få alvorlige bivirkninger, som for størstedelens vedkommende kan behandles.

5.2 Klinisk spørgsmål 2

5.2.1 Litteratur

De samme studier er anvendt til at belyse både klinisk spørgsmål 1 og klinisk spørgsmål 2. Der henvises til afsnit 5.1.1. Heri indgår 55 børn ud af de i alt 164 patienter. Fagudvalget bemærker, at fordelingen af tumortyperne er væsentligt forskellig fra voksenpopulationen. De pædiatriske patienter i studierne af larotrectinib har helt overvejende (> 90 %) enten infantil fibrosarkom eller ikke nærmere specificerede bløddelssarkomer.

5.2.2 Databehandling og analyse

De kliniske studier, SCOUT LOXO-TRK-15003 (NCT-02637687) og NAVIGATE LOXO-TRK-15002 (NCT-02576431) ligger til grund for ansøgers besvarelse. Disse studier, de tilhørende datasæt og cut-off datoer er beskrevet under klinisk spørgsmål 1 (afsnit 5.1.2). Fagudvalget sammenligner ikke data for larotrectinib med en anden systemisk behandling, da der ikke indgår pædiatriske patienter i doxorubicin-kontrolgruppen og kun meget få pædiatriske patienter i studiet af Rosen et al. 2020.

5.2.3 Evidensens kvalitet

Datagrundlaget for klinisk spørgsmål 2 adskiller sig ikke substantielt fra datagrundlaget for klinisk spørgsmål 1. Der henvises derfor til afsnit 5.1.3. Grundlæggende er der tale om de samme studier af larotractinib, som i klinisk spørgsmål 1 (se afsnit 5.1.3). Derfor vurderer Medicinrådet også her, at evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.2.4 Effektestimater og kategorier

I Tabel 5-8 fremgår effektestimaterne for larotrectinib, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for det kliniske spørgsmål. Oversigten inkluderer kun patienter, der ikke har primære CNS-tumorer. Patienter med primære CNS-tumorer analyseres separat under andre overvejelser (afsnit 6.1).

Tabel 5-8. Resultater for klinisk spørgsmål 2

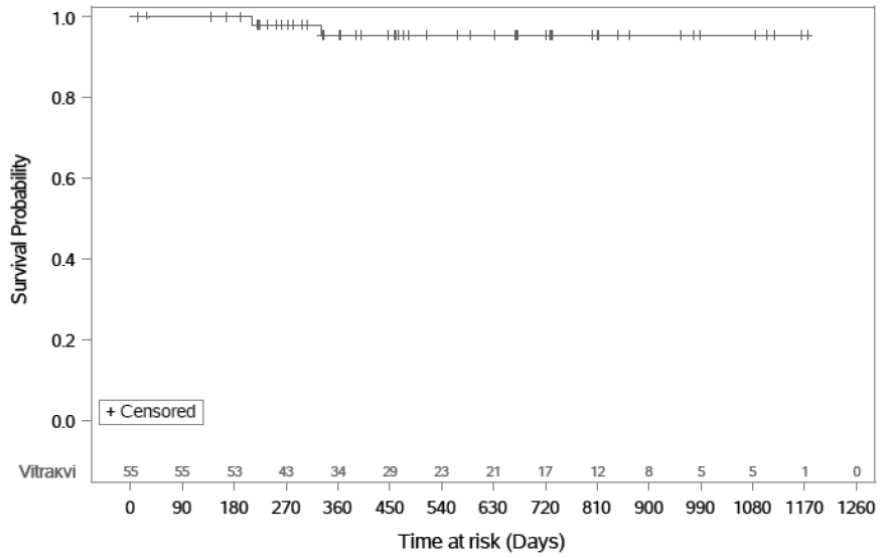
Effektmål	Målenhed (MKRF)	Vigtighed	Larotrectinib	Supplerende sammenligningsdata*		Aggregeret værdi for effektmålet
			Estimat [95 % CI]			
Overlevelse	Median OS i antal måneder (MKRF: 3 måneder)	Kritisk	Ikke nået	Ingen data	Ingen data	Kan ikke kategoriseres
	OS-rate ved 24 måneder (MKRF: 5 %)		95 % [89-100]	Ingen data	Ingen data	
	Andel patienter med komplet patologisk respons (MKRF: 5 %)		18,2 % (10 patienter)	Ingen data	Ingen data	
Livskvalitet	Forskel i gennemsnitlig ændring i PedsQL (MKRF: 4,5 point)	Kritisk	Ændring præ vs. post-baseline: 14,8 point (n = 24)	Ingen data	Ingen data	Kan ikke kategoriseres
Objektiv responsrate	Samlet ORR (MKRF: narrativ vurdering)	Vigtigt	94,5 %	Ingen data	Ingen data	Kan ikke kategoriseres
Progressionsfri overlevelse	Median PFS (MKRF: 3 måneder)	Vigtigt	Ikke nået	Ingen data	Ingen data	Kan ikke kategoriseres
	PFS-rate ved 12 måneder (MKRF: 10 %-point)		86 % [75; 97]	Ingen data	Ingen data	

Effektmål	Målenhed (MKRF)	Vigtighed	Larotrectinib Estimat [95 % CI]	Supplerende sammenligningsdata*		Aggregeret værdi for effektmålet
Uønskede hændelser	Andel patienter med én eller flere uønskede hændelser grad 3-4 (MKRF: 5 %-point)	Vigtigt	61 %**	Ingen data	Ingen data	Kan ikke kategoriseres
	Kvalitativ gennemgang af uønskede hændelser			Ingen data	Ingen data	

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget finder det sandsynligt, at larotrectinib er en effektiv behandling med acceptable bivirkninger til børn med NTRK-fusion-positive kræftformer, der ikke har andre tilfredsstillende behandlingsmuligheder.
Kvalitet af den samlede evidens	Meget lav.

* Der er ikke præsenteret supplerende sammenligningsdata, da der ikke er indsendt eller identificeret data, der er repræsentativt for børn med lignende kræftformer. ** Estimatet er fra den samlede bivirkningsoversigt over de 59 børn, der har modtaget larotrectinibbehandling.

Overlevelse
Medianoverlevelsen er endnu ikke nået for børn på dataopgørelsestidspunktet (median opfølgningstid på 15,3 måneder). Overlevelsesraten ved 24 måneder var 95 % (89-100 %). Ud af i alt 55 patienter døde to i opfølgningsperioden.



Figur 5-3. Overlevelse for pædiatriske patienter behandlet med larotrectinib.

I alt 10 ud af 55 patienter (18,2 %) opnåede komplet patologisk respons og afsluttede behandlingen med larotrectinib efter operation med kurativ hensigt. Disse patienter var inden behandling med larotrectinib ikke kandidater til kirurgi eller havde tumorudbredelse, som betød, at et kirurgisk indgreb ville medføre betragtelig morbiditet.

Samlet set vurderer fagudvalget, at larotrectinib har en betydelig effekt på overlevelsen for børn, på baggrund af både overlevelsesestimaterne og den høje andel af komplet patologisk respons. Den foreløbige værdi kan dog ikke kategoriseres pga. manglende sammenligningsgrundlag.

Livskvalitet
Livskvalitet for pædiatriske patienter er opgjort med *The Pediatric Quality of Life Inventory* (PedsQL). Den mindste klinisk relevante forskel er fastsat til 4,5 point.
I alt 24 børn er både evalueret før behandling og minimum én gang efter behandlingsstart. Gennemsnitsscore før behandling var 68,1 ± 21,4 og 82,9 ± 18,9 ved sidste opfølgende måling. Dette svarer til en stigning på 14,8 point ud fra punktestimatet, hvilket overstiger den mindste klinisk relevante forskel. Hele konfidensintervallet for sidste måling ligger over den mindste klinisk relevante forskel ([75; 91]), hvilket indikerer en klinisk meningsfuld øgning af livskvalitet efter behandling med larotrectinib. Fagudvalget vurderer, at de kliniske data tyder på en positiv effekt af behandlingen. Fagudvalget bemærker dog, at der mangler data fra mere end halvdelen

af patienterne, hvilket kan resultere i bias ift. den intraindividuelle ændring i livskvalitet før versus efter behandling med larotrectinib.

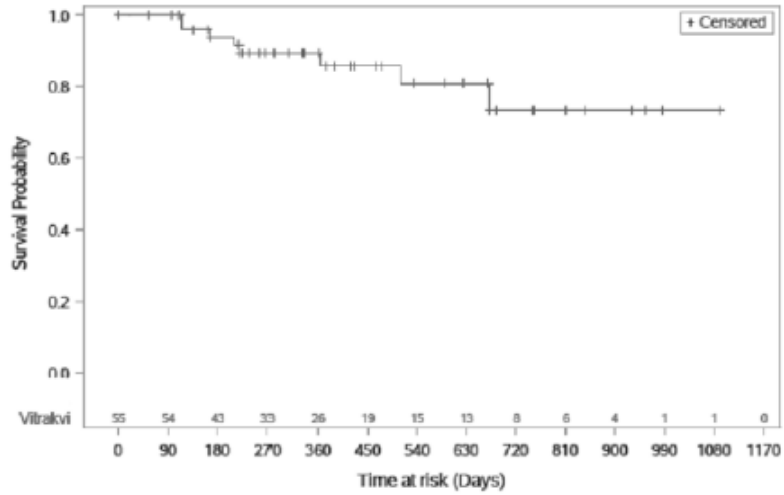
Larotrectinibs værdi for livskvalitet kan ikke kategoriseres, da der udelukkende foreligger data fra single-arm-studier.

Objektiv responsrate
De pædiatriske patienter havde en objektiv responsrate på 94,5 %. Af disse opnåede 36,0 % komplet respons, mens 58,5 % opnåede partielt respons.

Fagudvalget efterspurgte jf. protokollen en gennemgang af ORR per tumortype. Dette er ikke angivet separat for den pædiatriske population men kun for den samlede population (voksne og børn). Derfor behandles dette ikke yderligere her, men ORR per tumortype i den samlede population kommenteres under andre overvejelser (afsnit 6.3).

Ansøger har ikke indsendt materiale, der muliggør en naiv sammenstilling af larotrectinib overfor placebo. Den kliniske værdi af larotrectinib ift. placebo kan derfor ikke kategoriseres. Fagudvalget bemærker, at patienter, som ikke modtager aktiv behandling, må antages at have en objektiv responsrate tæt ved 0 %. Fagudvalget vurderer, at ORR for larotrectinib er meget høj. Der ses meget sjældent objektive responsrater på dette niveau på tværs af behandlingsformer for solide tumorer. Derudover har størstedelen af patienterne modtaget tidligere systemiske behandlinger (ca. 80 % af patienterne i den samlede population af børn og voksne), hvilket ofte medfører lavere responsrater i efterfølgende behandlingslinjer. Fagudvalget bemærker dog, at ORR ved infantilt fibrosarkom er 97 % (se afsnit 6.3), og at dette har bidraget til den høje samlede ORR for børn.

Progressionsfri overlevelse
Median progressionsfri overlevelse var ikke nået for pædiatriske patienter på dataopfølgningstidspunktet, hvor 8 ud af 55 patienter har progredieret. Ved 12 måneder var 86 % (75 - 97 %) af de pædiatriske patienter progressionsfri.



Figur 5-4. Progressionsfri overlevelse for pædiatriske patienter, der har modtaget behandling med larotrectinib

Der findes ikke et sammenligningsgrundlag til at vurdere larotrectinibs effekt på PFS for børn, og effekten kan derfor ikke kategoriseres. Fagudvalget vurderer dog, at det eksisterende data indikerer en lang PFS ved behandling med larotrectinib. Dette styrkes yderligere af, at størstedelen af patienterne oplevede en væsentlig længere PFS ved larotrectinibbehandlingen end ved deres foregående systemiske behandling (se afsnit 6.2 om GMI).

Uønskede hændelser

Ansøger har vedlagt en liste over samtlige uønskede hændelser i børn, der inkluderer alle børn med NTRK-fusion-positiv kræft, der har modtaget minimum én dosis larotrectinib (n = 59). Samlet set oplevede 61 % af patienterne minimum én grad 3-4-uønsket hændelse, mens det ikke er angivet, hvor mange der måtte dosisjusteres eller stoppe behandlingen. Fagudvalget bemærker, at resultater for andel af patienter med uønskede hændelser reflekterer akkumulation over en lang behandlingsperiode, hvilket er usædvanligt i en palliativ population.

De hyppigste uønskede hændelser hos børn generelt var pyreksi, kvalme/opkastning og øget niveau af alanin-aminotransferase, mens de hyppigste grad 3-4-uønskede hændelser var neutrocytopeni (23 %), vægtøgning (10 %), pyreksi (7 %) og anæmi (7 %). Den kliniske værdi af larotrectinib ift. placebo kan ikke kategoriseres.

Fagudvalget bemærker dog, at larotrectinib fremstår relativt skånsomt overfor andre hyppigt anvendte tyrosinkinasehæmmere. Desuden vurderer fagudvalget, at patienterne kan behandles for de grad 3-4-uønskede hændelser, som er forbundet med behandling med larotrectinib

5.2.5 Fagudvalgets konklusion vedr. børn

Den kliniske værdi af larotrectinib overfor placebo, til behandling af børn med NTRK-genfusion-positiv kræft, hvor øvrige tilfredsstillende behandlingsmuligheder er udtømte, kan ikke kategoriseres. Dette skyldes mangel på et komparativt datagrundlag. Fagudvalget finder det sandsynligt at larotrectinib er en effektiv behandling til børn med en acceptabel bivirkningsprofil hos børn. Dette er baseret på:

- Væsentlig forbedret overlevelse, baseret på at knap 20 % kunne betragtes som helbredte efter behandlingen, og at den samlede gruppe havde 2-års overlevelse på 95 %.
- Meget høje responsrater (95 %) og lang PFS.
- En statistisk signifikant og klinisk relevant øget livskvalitet for børn under behandlingen med larotrectinib.
- Få alvorlige bivirkninger, som for størstedelens vedkommende kan behandles.

Fagudvalget lægger særligt vægt på, at 10 patienter med infantilt fibrosarkom ud af i alt 55 pædiatriske patienter opnåede komplet patologisk respons. Dette skal dog ses i lyset af, at infantilt fibrosarkom generelt er relativt responsivt overfor kemoterapi og er forbundet med en god prognose [24].

Fagudvalget bemærker, at de pædiatriske patienter i studierne af larotrectinib helt overvejende (> 90 %) har enten infantil fibrosarkom eller ikke nærmere specificerede bløddelssarkomer.
Samlet set vurderer fagudvalget, at det forhåndenværende non-komparative data indikerer, at larotrectinib er et væsentligt bedre behandlingsalternativ end placebo.

6. Andre overvejelser

6.1 Data fra patienter med primære CNS-tumorer

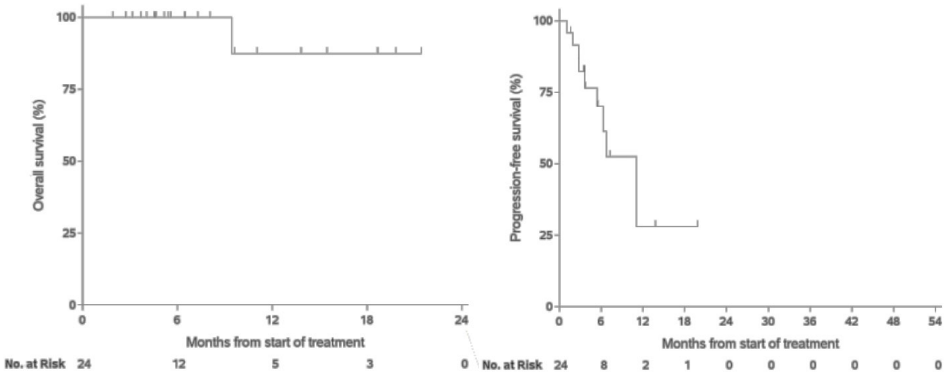
I protokollen efterspurgte fagudvalget, at data fra patienter med primære CNS-tumorer skulle indgå i de samlede analyser, da de kliniske spørgsmål er baseret på en vævsagnostisk indikation. Ansøger har valgt ikke at inkludere disse data i de samlede effektanalyser og begrunder sit valg med, at tumorprogression og respons evalueres anderledes end for perifere tumorer. Ansøger har i stedet indsendt data specifikt for de 24 patienter.

Fagudvalget finder det beklageligt, at opdelingen ikke er i overensstemmelse med protokollen, men har vurderet effekten på primære CNS-tumorer separat. Fagudvalget bemærker dog, at eventuelle anbefalinger vedr. ibrugtagning bør tage højde for, at gennemgangen af data for klinisk spørgsmål 1 og 2 *ikke* inkluderer patienter med primære CNS-tumorer.

I de kliniske studier med larotrectinib indgik 24 patienter med primære CNS-tumorer. Dette var hovedsageligt børn (83 %) og medianalderen var 8 år (1,3-79 år).

Ansøger har kun indsendt data for OS, PFS og ORR. Fadvalget vurderer, at uønskede hændelser for patienter med primære CNS-tumorer vil svare til data for patienter med tumorer udenfor CNS. Livskvaliteten formoder fagudvalget dog kan være væsentlig påvirket af behandlingens effekt.

Median OS var ikke nået, og OS-raten ved 24 måneder kunne ikke beregnes, da ingen patienter har været fulgt tilstrækkeligt længe. Medianopfølgningstiden var 5,3 måneder. Ved data cut-off er der rapporteret et dødsfald. Median PFS var 11 måneder, og PFS-raten ved 12 måneder var ca. 30 % (aflæst fra Figur 6-1).



Figur 6-1. Data for effektmål fra 24 patienter med primær CNS-tumor. Venstre: overlevelse (OS); højre: progressionsfri overlevelse (PFS).

PFS i CNS-tumorgruppen er væsentlig kortere end gruppen af pædiatriske patienter med perifere tumorer, både i forhold til median PFS (ikke nået for børn generelt overfor 11 måneder hos patienter med CNS-tumorer) og PFS raten ved 12 måneder (86 % overfor 30 %).

ORR ved CNS-tumorer angives af ansøger til 21 % [17], hvoraf 8,4 % opnåede komplet respons og 12,6 % partielt respons. Det er uklart, i hvor høj grad dette kan sammenlignes med ORR i børnepopulationen generelt, da tumorrespons er vurderet ud fra andre kriterier ved CNS-tumorer. Alligevel vurderer fagudvalget, at ORR er markant lavere hos patienter med primære CNS-tumorer end for børnepopulationen generelt (21 % overfor 94,5 %).

Fagudvalget vurderer, at larotrectinib fremstår mindre effektivt i patienter med primære CNS-tumorer end hos patienter med primære tumorer udenfor CNS.

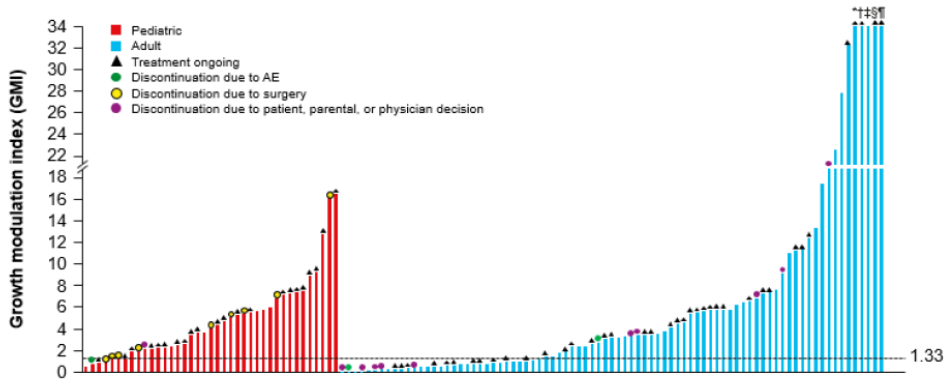
6.2 Growth modulation index

Fagudvalget har, i forventning om manglende komparativt data, i protokollen bedt ansøger indsende data for *growth modulation index* (GMI). GMI er en 'før-og-efter' intrapatient-analyse, som beskriver ratioen imellem patienternes tid til progression (TTP) på entrectinib og patienternes TTP på den behandling, de modtog umiddelbart inden (forskellige præparater fra patient til patient). Analysen fortæller således kun noget om

larotrectinibs effekt i relation til den forudgående behandling. Hvis TTP for interventionen er lig med TTP for den forudgående behandling, er GMI = 1. Er TTP længere for interventionen end for den forudgående behandling, vil GMI være > 1 og omvendt. I litteraturen er en GMI-ratio på 1,33 fremhævet som en meningsfuld om end arbitrær tærskelværdi. GMI er et relativt effektmål, så en GMI på 1,33 kan både dække over f.eks. en median PFS-gevinst på 3,3 måneder (hvis TTP på forudgående behandling var 10 måneder) eller 0,3 måneder (hvis TTP på den forudgående behandling var 1 måned). GMI skal fortolkes i lyset af, at TTP som hovedregel vil være kortere i senere behandlingslinjer sammenlignet med tidligere behandlingslinjer.

Ansøger har indsendt en analyse, som blev præsenteret som poster på ESMO kongressen 2020 [22]. Der er ikke indsendt kvantitative data, om hvilke lægemidler patienterne blev behandlet med forud for larotrectinib. Det er dog værd at bemærke, at 22 % af patienterne ikke modtog nogen systemisk behandling inden larotrectinib, hvorfor den indsendte GMI-analyse kun indeholder data fra de resterende 78 % (n = 122). De indsendte data indeholder både en samlet analyse af hele populationen samt delanalyser af voksne (n = 83) og børn (n = 39).

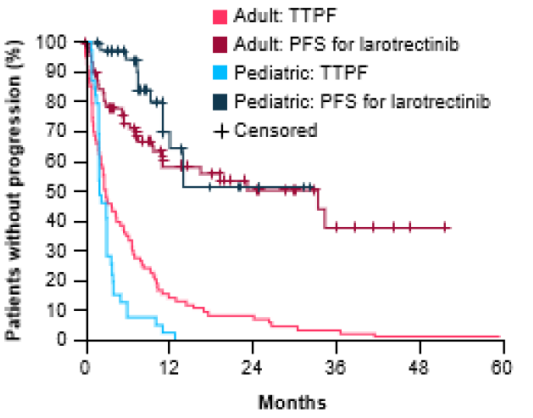
Jf. ansøgers analyse var den mediane GMI for larotrectinib versus den forudgående behandling 3,35 (rækkevidde: 0 til 337, gennemsnit: 10,8), hvis man ser på den samlede population. Ansøger har ikke udregnet medianværdier for børn og voksne separat, men har indsendt data i et waterfall plot (Figur 6-2).



Figur 6-2: Growth modulation index for børn (rød) og voksne (blå). Figuren stammer fra en poster præsenteret på ESMO 2020 [22].

Heraf fremgår det, at størstedelen af patienterne oplever en GMI over 1,33, hvilket gælder både voksne (63 %) og børn (82 %), og medianerne kan aflæses til ca. 3,5 for voksne og 4 for børn. Her er det værd at bemærke, at børn med komplet patologisk respons er medtaget i denne beregning, hvorved GMI trækkes i en mere negativ retning, da disse patienters fulde potentiale for PFS med larotrectinib ikke er medregnet. Fagudvalget konstaterer, at der ses en klart forøget PFS ved larotrectinib i forhold til den før kommende behandlingslinje for hovedparten af patienterne.

Ansøger har desuden indsendt et Kaplan-Meyer plot, der viser PFS for behandling med larotrectinib samt TTP ved den umiddelbart forudgående behandling inddelt efter voksne og børn (Figur 6-3). For voksne var median TTP 3 måneder, mens PFS på larotrectinib var 33,4 måneder. Dette resulterede i en HR på 0,27 [0,18; 0,40]. For børn var median TTP 2 måneder, mens PFS på larotrectinib ikke var nået, hvilket resulterede i en HR på 0,07 [0,03; 0,16].



	Adult		Pediatric	
Median, months (95% CI)	3.0 (2.3, 5.1)	33.4 (10.9, NE)	2.0 (2.0, 3.0)	NR
HR (95% CI)	0.27 (0.18, 0.40)		0.07 (0.03, 0.16)	

Figur 6-3. Kaplan-Meier-kurver for PFS ved behandling med larotrectinib samt TTP for den forudgående behandlingslinje for hhv. børn og voksne. Figuren stammer fra en poster præsenteret på ESMO 2020 [22].

Fagudvalget vurderer, at der er evidens for, at patienterne har væsentlig længere tid til sygdomsprogression ved behandling med larotrectinib end ved den behandling, de har modtaget umiddelbart inden. Der tages forbehold for, at analysen pr. design er forbundet med væsentlig usikkerhed, herunder at sammenligningen bygger på data fra to forskellige behandlingslinjer. Fagudvalget lægger vægt på, at tid til progression ved behandling af solide tumorer typisk vil være kortere i senere behandlingslinjer end tidligere.

6.3 Objektivt respons pr. tumortype

Ansøger har indsendt data, der viser ORR opdelt per tumortype for den samlede population. Disse data er også tilgængelige i EMAs opdaterede produktresumé.
I protokollen blev der efterspurgt data for hver inkluderet kræftdiagnose opdelt på voksne og børn. Ansøger har ikke indsendt disse men argumenterer for, at dette ville medføre for små grupper til at kunne udlede meningsfulde estimater. Ansøger har i stedet indsendt en gennemgang af ORR per tumortype baseret på den samlede patientpopulation fra ePAS4-datasættet. De enkelte responsrater samt antallet af patienter med de pågældende tumortyper er vist i tabellen nedenfor [17].

Tabel 6-1. Oversigt over objektiv responsrate (ORR) opgjort per tumortype i den samlede patientpopulation inklusive patienter med primær CNS-tumor

Tumortype	Antal patienter (n = 188)	ORR %	95 % CI
Bløddelssarkom[1, a]	36	81 %	64; 92
Infantilt fibrosarkom [a]	32	97 %	84; 100
Skjoldbruskkirtelkræft [a]	27	56 %	35; 75
Primær CNS-tumor [b]	24	21 %	7; 42
Spytkirtelkræft [a]	21	86 %	64; 97
Lungekræft [a]	13	77 %	46; 95
Kolorektalkræft [a]	8	38 %	9; 76
Melanom [a]	7	43 %	10; 82
Brystkræft [a]	5	60 %	15; 95
Gastrointestinal stomal tumor (GIST) [a]	4	100 %	40; 100
Knoglesarkom [a]	2	50 %	1; 99
Kolangiokarcinom [a]	2	SD, NE (0 %)	-
Bugspytkirtelkræft [a, c]	2	SD, SD (0 %)	-
Kongenit mesoblastisk nefrom [a]	1	100 %	3; 100
Kræft med ukendt primær lokation	1	100 %	3; 100
Blindtarmskræft [a]	1	SD (0 %)	-
Leverkræft	1	NE (0 %)	-
Prostatakræft	1	PD (0 %)	-

[1] Fraset infantilt fibrosarkom samt GIST. [a] Uafhængig opgørelse via. RECIST v 1.1, [b] Opgjort enten via RECIST v1.1 eller RNAO, [c] 3 patienter med non-sekretorisk tumor (2 i respons) og 2 med sekretorisk tumor (1 respons). Tabellen er fra produktresuméet [17]. PD = progressiv sygdom (*progressive disease*), SD = stabil sygdom (*stabile disease*), NE = ikke estimeret (*not estimated*).

I alt 9 af tumortyperne var repræsenteret af mindre end 5 patienter. Fagudvalget vurderer, at det for disse ikke er meningsfyldt at evaluere ORR. For de resterende 9 tumortyper repræsenteret ved minimum 5 patienter (5-36) sås varierende ORR fra 21 % (primære CNS-tumorer, n = 24) til infantilt fibrosarkom (97 %, n = 32). Fraset CNS-tumorer ses de laveste ORR ved kolorektalkræft (38 %, n = 8), melanom (43 %, n = 7 patienter) og thyroideakræft (56 %, n = 27 patienter). Datagrundlaget for disse tumortyper er ikke stærkt nok til at kunne konkludere, om effekten adskiller sig i negativ retning fra den gennemsnitlige ORR – i alle tilfælde inkluderer konfidensintervallerne for ORR i specifikke tumortyper punktestimatet for den samlede population af voksne

patienter. Fagudvalget bemærker dog, at ORR ved infantilt fibrosarkom er 97 % [84; 100], og at dette har bidraget til den høje samlede ORR for børn.

6.4 Screening for NTRK-fusion

Der findes en række foreslåede strategier, for hvordan screening for NTRK-fusioner bør foregå [25,26]. Fagudvalget vurderer, at følgende er en hensigtsmæssig fremgangsmåde til at teste for NTRK-fusioner i danske patienter:

Indledende screening kan foretages ved brug af immunohistokemi (IHC). Påvises NTRK-fusion ved IHC, bør det følges op med *next generation sequencing* (NGS) mRNA-fusionsanalyse, hvor analysen er uafhængig af fusionspartner. Indledende screening kan også foretages med NGS for andre driver-mutationer. Ved negativt resultat af NGS for andre driver-mutationer bør der ligeledes følges op med NGS mRNA-fusionsanalyse, hvor analysen er uafhængig af fusionspartner.

I histologier, hvor NTRK-fusioner hyppigt forekommer med en kendt fusionspartner, kan fluorescense in situ hybridization (FISH) anvendes som primær screeningsmetode. Ved negative resultater af FISH bør der følges op med NGS af mRNA, hvor kendskab til fusionspartner ikke er påkrævet.

Ved udelukkende at anvende NGS af mRNA med en metode, der er uafhængig af fusionspartneren, kan man undgå at teste ad flere omgange og opnå det mest præcise resultat. Dette skal dog vejes op imod pris og tilgængelighed.

Generelt gælder det, at screening som udgangspunkt kun bør finde sted hos patienter, hvor der er klinisk indikation for anvendelse af NTRK-fusionshæmmere. Undtagelser inkluderer dog kræfttyper, hvor der allerede foretages relevant NGS-screening *up front,* og hvor denne evt. kan udvides til også at screene for NTRK-fusioner.

For yderligere overvejelser vedr. screeningsmetodik henvises der til bilag 2.

6.5 ESMO-MCBS-vurdering

Fagudvalget har foretaget en ESMO *magnitude of clinical benefit scale* (MCBS)-vurdering baseret på ePAS4-datasættet. ESMO-MCBS-formular nr. 3 er anvendt (single-arm-studier). ESMO-MCBS rangerer fra 1 (laveste '*magnitude of clinical benefit*') til 5 (højeste '*magnitude of clinical benefit*'). Den kliniske værdi ved score 4 og 5 beskrives som værende substantiel. Larotrectinib indplaceres med en score på 3. Baseret på ansøgers opgørelse af livskvalitet er det usikkert, om patienter oplever forbedret helbredsrelateret livskvalitet efter behandling med larotrectinib, hvorfor dette domæne ikke kan anvendes i vurderingen. ESMO-MCBS-vurderingen er vedlagt som bilag 3.

7. Fagudvalgets samlede konklusion

Værdien af larotrectinib overfor placebo til behandling af voksne og børn med NTRK-fusion-positiv kræft kan ikke kategoriseres ved brug af Medicinrådets metoder pga. manglende komparativt datagrundlag.

Fagudvalget finder det sandsynligt, at larotrecinib er en effektiv behandling med få tålelige bivirkninger til voksne og børn, med forskellige kræftsygdomme, der ikke har andre tilfredsstillende behandlingsmuligheder. Dette er baseret på:

- Lang overlevelse hos både børn og voksne og dokumenteret komplet patologisk respons hos knap 20 % af børnene.
- Høje responsrater og lang PFS i både børn og voksne.
- Bedring af livskvalitet hos børn, og ikke forværring af livskvalitet hos voksne.
- Relativt få alvorlige bivirkninger, der for størstedelens vedkommende kan behandles.
- Data fra GMI-analysen der viser, at larotrectinib er væsentligt mere effektivt end den behandling patienterne modtog i den umiddelbart forudgående behandlingslinje.

Fagudvalget bemærker yderligere, at larotrectinib scorer højt i ESMO-MCBS-vurderingen (bilag 3).

Vurderingen af larotrectinib er baseret på evidens af meget lav kvalitet.
Fagudvalget bemærker, at det på grund af sjældenheden af NTRK-fusion og larotrectinibs vævsagnostiske indikation er vanskeligt at foretage en nøjagtig vurdering af larotrectinibs kliniske værdi ud fra Medicinrådets metoder.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Lars Henrik Jensen *Overlæge*	Region Syddanmark og Dansk Selskab for Klinisk Onkologi
Medlemmer	**Udpeget af**
Morten Ladekarl *Professor, overlæge, dr.med.*	Region Nordjylland
Anni Ravnsbæk Jensen *Ledende overlæge*	Region Midtjylland
Pernille Wendtland *Overlæge*	Region Midtjylland
Karin Holmskov Hansen *Overlæge*	Region Syddanmark
Eckhard Schomerus *Overlæge*	Region Syddanmark
Karen Julie Gehl *Professor, Overlæge, dr.med.*	Region Sjælland
Martin Højgaard *Afdelingslæge, ph.d.*	Region Hovedstaden
Lisa Sengeløv *Ledende overlæge, dr.med.*	Region Hovedstaden
Troels K. Bergmann *Overlæge, klinisk lektor (speciallæge i klinisk farmakologi)*	Dansk Selskab for Klinisk Farmakologi
Torben Steiniche *Professor, overlæge, dr.med.*	Dansk Patologiselskab
Karsten Nielsen *Overlæge, lektor, dr.med.*	Dansk Patologiselskab

Sammensætning af fagudvalg	
Simone Møller Hede *Patient/patientrepræsentant*	Danske Patienter
Diana Kristensen *Patient/patientrepræsentant*	Danske Patienter
Tidligere medlemmer, som har bidraget til arbejdet	**Udpeget af**
Ruta Tuckuviene *Overlæge, speciallæge i børneonkologi*	Region Nordjylland

Medicinrådets sekretariat

Medicinrådet
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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. maj 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Studiekarakteristika for de inkluderede studier

LOXO-TRK-14001 er et fase I-studie med det formål at bestemme sikkerhed, farmakokinetik og anbefalet dosis af larotrectinib til patienter med kræft med NTRK-fusion.

Tabel 12-1. Studiekarakteristika for LOXO-TRK-14001

Studie (NCT-nummer)	LOXO-TRK-14001 (NCT-02122913)
Fase og studietype	Fase I, randomiseret til to doser (dosisekspansionskohorten).
Patientgruppe (n)	Voksne (75).
Beskrivelse	Bestemmelse af sikkerhed, farmakokinetik og anbefalet dosis af larotrectinib i patienter med faste tumorer med NTRK-fusioner.
Start- og slutdato	4. maj 2014 – 1. februar 2017 / 30. marts 2021 (actual primary / estimate).
Primært effektmål	Antal patienter, der oplever bivirkninger og bivirkningers alvorlighed. Maximalt tolererede dosis. Anbefalet dosis.
Behandlingsregime	Patienter modtog larotrectinib oralt (som kapsler eller i flydende form) i koncentrationer fra 50-200 mg én gang dagligt eller 150-200 mg to gange dagligt i cykler af 28 dage for bestemmelse af maksimalt tolererede dosis (dosiseskalationskohorte). Patienter modtog enten 100 mg larotrectinib 2 gange dagligt i cykler af 28 dage eller den maksimalt tolererede dosis (dosisekspansionskohorte).
Vigtigste inklusionskriterier	Voksne patienter med lokalt fremskreden eller metastatisk kræft, som har progredieret, eller som ikke har responderet på tilgængelig behandling. Fremskreden solid tumor til dosiseskalation og påvist NTRK-fusion til dosisekspansion. ECOG-score mellem 0-2 med forventet levetid på mindst 3 måneder. Sufficient hæmatologisk funktion, nyre- og leverfunktion.
Eksklusionskriterier	Patienter med ustabile primære CNS-tumorer eller CNS-metastaser (mulighed for undtagelser). Klinisk relevant hjerte-kar-sygdom eller tidligere myokardieinfarkt. Aktive ukontrollerede systemiske infektioner. Aktuel behandling med en stærk CYP3A4-inhibitor eller aktivator. Graviditet eller amning.

SCOUT-LOXO-TRK-15003 er et fase I/II-studie i børn med det formål at bestemme sikkerhed, farmakokinetik og anbefalet dosis af larotrectinib til patienter med kræft med NTRK-fusion:

Tabel 12-2. Studiekarakteristika for LOXO-TRK-15003

Studie (NCT-nummer)	**SCOUT LOXO-TRK-15003 (NCT-02637687)**
Fase og studietype	Fase I/II. Ikke randomiseret (basket trial).
Patientgruppe (n)	Børn og voksne op til 21 år (174)*.
Beskrivelse	Fase I: Bestemmelse af effekt, sikkerhed og farmakokinetik af larotrectinib hos børn med kræft med lokalt fremskreden eller metastatisk solid tumor eller primær CNS-tumor, hvortil der ikke findes andre kurative behandlingsalternativer. Fase II: Bestemmelse af hvor godt og hvor længe forskellige cancertyper med NTRK-fusion responderer på larotrectinib.
Start- og slutdato	16. december 2017 – 30. september 2026.
Primært effektmål	Fase I: Bivirkninger (antal og alvorlighed). Fase II: Objektiv responsrate (ORR).
Behandlingsregime	Patienter modtog larotrectinib oralt (som kapsler eller i flydende form) i koncentrationer svarende til en voksendosis fra 50-150 mg to gange dagligt eller 100-200 mg/m^2 to gange dagligt i cykler af 28 dage for bestemmelse af maksimalt tolererede dosis (dosiseskalationskohorte). Patienter modtog 100 mg/m^2 larotrectinib 2 gange dagligt i cykler af 28 dage (dosisekspansionskohorte).

Studie (NCT-nummer)	SCOUT LOXO-TRK-15003 (NCT-02637687)
Vigtigste inklusionskriterier	Fase I, dosiseskalation: Voksne under 21 år og pædiatriske patienter med lokalt fremskreden eller metastatisk kræft (faste tumorer) eller primære CNS-tumorer, der er recidiverende, har progredieret, eller som ikke har responderet på tilgængelig behandling, eller hvor der ikke findes en standard- eller tilgængelig kurativ behandling. Nyfødte med tumorer med påvist NTRK-fusion, der har progredieret, eller som ikke har responderet på tilgængelig behandling, eller hvor der ikke findes en standard- eller tilgængelig kurativ behandling. Patienter med lokalt avanceret infantilt fibrosarkom, hvor der ellers kun kan tilbydes amputation eller mutilerende kirurgi for at opnå komplet resektion. For dosisekspansion gælder udover ovenstående, at NTRK-fusion skal være påvist. Fase II: Som for Fase I, dosisekspansion. Desuden inkluderes: Patienter over 21 år med kræft med typisk pædiatrisk histologi. Patienter med godartede tumorer med påvist NTRK-fusion. Fase I og II: Patienter med primære CNS-tumorer eller cerebrale metastaser. For alle patienter gælder: Karnovsky- eller Lansky-resultater over 50. Tilstrækkelig hæmatologisk-, nyre- og leverfunktion.
Eksklusionskriterier	Klinisk relevant hjerte-kar-sygdom, tidligere myokardieinfarkt eller forlænget QT-interval. Aktive ukontrollerede systemiske infektioner (bakteriel-, viral- eller svampeinfektion). Aktuel behandling med en stærk CYP3A4-inhibitor eller aktivator. For Fase II desuden: Tidligere progression under behandling med en TRK-inhibitor.

*Studiet er igangværende. Det angivne patientantal afspejler den planlagte studiepopulation.

Navigate LOXO-TRK-15002 er et fase II-studie med det formål at undersøge larotrectinibs effekt som behandling for kræft med faste tumorer med NTRK-fusion:

Tabel 12-3. Studiekarakteristika for LOXO-TRK-15002

Studie **(NCT-nummer)**	**NAVIGATE LOXO-TRK-15002** **(NCT-02576431)**
Fase og studietype	Fase II, ikke randomiseret (basket trial).
Patientgruppe (n)	Børn over 12 år og voksne (203)*.
Beskrivelse	Undersøge larotrectinibs effekt som behandling for kræft med faste tumorer med NTRK-fusion.
Start- og slutdato	30. september 2015 – 15. august 2023 / 30. september 2025 (primary completion/study completion).
Primært effektmål	Objektiv responsrate (ORR).
Behandlingsregime	Patienter modtog 100 mg larotrectinib 2 gange dagligt i cykler af 28 dage.
Vigtigste inklusionskriterier	Patienter med lokalt fremskreden eller metastatisk kræft med NTRK-fusion, der tidligere har modtaget standardbehandling for deres sygdom, eller som ikke vurderes at kunne klare eller have gavn af standardbehandlingen. Patienter skal have mindst én målbar læsion defineret af RECIST v. 1.1.
Eksklusionskriterier	Tidligere progression under behandling med TRK-inhibitor. Symptomatiske eller ustabile CNS-metastaser. Aktiv, ukontrolleret systemisk infektion. Ustabil hjerte-kar-sygdom. Andre systemiske sygdomme, der forhindrer, at behandlingen følges efter protokollen. Graviditet og amning.

*Studiet er igangværende. Det angivne antal afspejler den planlagte studiepopulation.

Bilag 2: Screening for NTRK-fusion

NTRK-fusioner opstår ved større kromosomale forandringer, som resulterer i at 3'-enden af NTRK-genet fusioneres med 5'-enden af en fusionspartner. 5'-enden af NTRK-genet koder for ligandbindingsdomænet, og når dette erstattes af 5'-enden af fusionspartneren, kan en konstitutivt aktiv TRK-receptor opstå, der signalerer uafhængigt af ligandbinding [27]. Der kendes mere end 80 forskellige NTRK-fusionspartnere, og forskellige fusionspartnere er kendt for henholdsvis NTRK1/2/3 [27,28].

NTRK-fusioner kan detekteres ved at teste DNA, mRNA eller protein fra en vævsprøve og kan detekteres ved en række forskellige metoder, herunder *fluorescense in situ hybridization* (FISH*), next generation sequencing* (NGS), immunohistokemi (IHC) og *reverse transcriptase polymerase chain reaction* (RT-PCR) (dog kun ved kendt fusionspartner og breakpoint). Metoderne adskiller sig fra hinanden i følsomhed/detektionsniveau, tilgængelighed og pris, se nærmere herom i [27].
For langt størstedelen af patienterne i larotrectinibs udviklingsprogram er deres NTRK-fusion detekteret med NGS af DNA eller mRNA (EPAR s. 14-15 samt s. 105 [11]).
I Danmark anvendes ofte FISH, IHC og NGS til screening for genændringer hos kræftpatienter. Der screenes i dag ikke rutinemæssigt for NTRK-fusioner.

IHC har lav specificitet men en tilstrækkelig sensitivitet til at kunne fungere som indledende screeningsmetode. IHC detekterer overekspression af NTRK-proteiner, og et positivt resultat bør følges op med NGS for at bekræfte, at overekspression skyldes en NTRK-fusion. FISH kan identificere NTRK-fusioner med kendte fusionspartnere og er anvendeligt som primær screeningsmetode i histologier, hvor NTRK-fusioner hyppigt forekommer med en kendt fusionspartner. Et negativt resultat for FISH bør dog følges op med NGS af mRNA med et assay, der er uafhængigt af fusionspartner. Påvisning af andre driver-mutationer kan også fungere som en primær screeningsmetode, idet tilstedeværelse af sådanne i langt de fleste tilfælde vil udelukke NTRK-fusioner.
NGS kan foretages af genomisk DNA eller mRNA. NGS af DNA kan detektere en lang række fusioner afhængigt af, hvilket assay der anvendes men kan på nuværende tidspunkt ikke detektere alle mulige fusioner (EPAR s. 14-15) [11]. Selvom NGS af genomisk DNA allerede foretages for en række kræftformer, vil disse analyser ikke nødvendigvis kunne udvides til at detektere NTRK-fusioner. For de fleste kræftformer (f.eks. NSCLC, kolorektalkræft, ovariekræft og hjernetumorer), hvor der allerede screenes med NGS, foregår analysen af genomisk DNA.

NGS af mRNA foretages i dag kun rutinemæssigt for ganske få kræftformer, f.eks. NSCLC, hvor der screenes for ALK og ROS1-fusioner. En del af de kits, som i dag anvendes til påvisning af mRNA-fusioner, kan kun påvise NTRK-fusioner med kendt fusionspartner eller give indikation omkring tilstedeværelse af en evt. NTRK-fusion via et såkaldt 5´-3´ *imbalance assay*. NTRK-fusioner kan påvises med sikkerhed ved mRNA-sekventering ved brug af et assay, der er uafhængigt af fusionspartner.

NGS vil typisk være tilgængeligt uafhængigt af behandlingssted men foregår oftest på Universitetshospitalerne.

Bilag 3: ESMO-MCBS

Fagudvalget beskrev i protokollen, at de ville anvende ESMO's vurderingsværktøj, *Magnitude of Clinical Benefit Scale*, som supplement til vurderingen, hvis ikke ansøger identificerede relevante studier til at belyse den komparative prognose. Fagudvalget har udfyldt ESMO-MCBS-Form 3 på baggrund af data fra LOXO-, SCOUT- og NAVIGATE-studierne.

ESMO-MCBS

ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1
EVALUATION FORM 3

For single-arm studies in "orphan diseases" and for diseases with "high unmet need" when primary outcome is PFS or ORR

Name of study:	LOXO, SCOUT, NAVIGATE				
Study medicine:	Larotrectinib	**Indication:**	Cancer with NTRK-fusion		
First author:	Drilon et al., Hong et al.	**Year:**	2018-20	**Journal:**	NEJM
Name of evaluator:	Fagudvalg vedr. tværgående kræftlægemidler				

GRADE 3	PFS ≥6 months	✓
	ORR (PR+CR) ≥60%	
	ORR (PR+CR) ≥20-<60% AND DoR ≥9 months	
GRADE 2	PFS ≥3-<6 months	
	ORR (PR+CR) ≥40-<60%	
	ORR (PR+CR) ≥20-<40% AND DoR ≥6-<9 months	
GRADE 1	PFS 2-<3 months	
	ORR(PR+CR) ≥20-<40% AND DoR <6 months	
	ORR (PR+CR) >10-<20% AND DoR ≥6 months	

Mark with √ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	3	2	1
	✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

CR, complete response; DoR, duration of response; ORR, overall response rate; PFS, progression-free survival; PR, partial response

ESMO-MCBS

Quality of life/Grade 3-4 toxicities* assessment

Was QoL evaluated as secondary outcome?	✓
Does secondary endpoint QoL show improvement?	
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc. Mark with √ if relevant

Adjustments

A	Downgrade 1 level if there are ≥30% grade 3-4 toxicities impacting on daily well-being*
B	Upgrade 1 level if improved QoL
C	Upgrade 1 level for confirmatory, adequately sized, phase 4 experience

Final adjusted magnitude of clinical benefit grade	4	3	2	1
		✓		

Non-curative setting grading - 5 and 4 indicates a substantial magnitude of clinical benefit

QoL, quality of life

Bemærk: På det forhåndenværende datagrundlag er det uklart, om larotrectinib resulterer i relevant forbedret helbredsrelateret livskvalitet. Data indikerer, at dette er tilfældet hos børn, hvorved scoren ville være 4, mens data for voksne er inkonklusive.

Final application
for the assessment of Vitrakvi® (larotrectinib)

The medical section

Vitrakvi® as monotherapy is indicated for the treatment of pediatric and adult patients with solid tumors that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion:

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity
- who have no satisfactory treatment options.

Contents

1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Vitrakvi®
Generic name	Larotrectinib
Marketing authorization holder in Denmark	23-09-2019
ATC code	L01XE53
Pharmacotherapeutic group	Antineoplastic Agents
Active substance(s)	Larotrectinib sulfate
Pharmaceutical form(s)	Capsules and oral solution
Mechanism of action	Vitrakvi® is an adenosine triphosphate (ATP) competitive and selective tropomyosin receptor kinase (TRK) inhibitor that was selectively designed to avoid activity with off target kinases. The target for Vitrakvi® is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes, respectively (Vitrakvi® SmPC 2019). In a broad panel of purified enzyme assays, Vitrakvi® inhibited TRKA, TRKB, and TRKC with IC_{50} values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations. In in vitro and in vivo tumor models, Vitrakvi® demonstrated anti-tumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. Vitrakvi® demonstrated potent inhibition of TRK proteins and inhibition of proliferation of tumor cells in a concentration-dependent manner (Vitrakvi® SmPC 2019).
Dosage regimen	*Adults* The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. *Pediatric population* Dosing in pediatric patients is based on body surface area (BSA). The recommended dose in pediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Vitrakvi® as monotherapy is indicated for the treatment of adult and pediatric patients with solid tumors that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion who, • have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory treatment options.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Packaging – types, sizes/number of units, and concentrations	Capsules (two pack sizes: 56 capsules a 25mg and 56 capsules a 100mg) and oral solution (100ml a 20 mg/ml)
Orphan drug designation	N/A

2 Abbreviations

ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BOR	Best overall response
BRAF	B-Raf proto-oncogene
BSA	Body surface area
BSC	Best supportive care
CEM	Cost-effectiveness model
CMN	Congenital mesoblastic nephroma
CNS	Central Nevous System
CR	Complete response
CRC	Colorectal cancer
DOR	Duration of response
ECG	Electrocardiography
EMA	European medicines agency
ePAS4	Extended primary analysis set 4 (n=164)
GBM	Glioblastoma multiforme
GIST	Gastrointestinal stromal tumor
GMI	Growth modulation index
HRQoL	Health-related quality-of-life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFS	Infantile fibrosarcoma
INV	Investigator
IRC	Independent review committee
KIT	Tyrosine-protein kinase KIT
LDH	Lactate dehydrogenase
LoE	Loss of exclusivity
LVEF	Left ventricular ejection fraction
MA	Marketing authorization
MASC	Mammary-analogous secretory carcinoma
PMRM	Pooled Model Repeated Measures
MUGA	Multigated acquisition scan
NE	Not estimated/estimable
NR	Not reported/reached
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase receptor
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Primary analysis set (n=55)
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
QALY	Quality-adjusted life-years
QoL	Quality of life
RANO	Response assessment in neuro-oncology criteria
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SmPC	Summary of product characteristics
STS	Soft-tissue sarcoma
TMB	Tumor mutational burden
TRK	Tropomyosin receptor kinase
TTP	Time to progression

The Medical Application

3 Summary

Vitrakvi® is an orally bioavailable and highly selective TRK inhibitor that provides a rapid and durable outcome for patients with TRK fusion cancer, a rare disease within oncology. The target for Vitrakvi® is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively. It is the first cancer drug to be EMA approved in a histology independent indication.

The common denominator for all tumors is the detection of NTRK gene fusions. All patients included in the Vitrakvi® trials have a locally advanced or metastatic solid tumor. They have previously received standard of care or later-line chemo therapies and have no other satisfactory anti-tumoral treatment options available. Thus, Vitrakvi® is developed for a very specific population with a high unmet medical need. Current treatment modalities for patients with a locally advanced, metastatic tumour without any satisfactory anti-tumoral treatment option is mainly last line chemotherapy, most often doxorubicin.

The Vitrakvi® indication is tumor agnostic in a rare cancer based on data which demonstrate durable efficacy across tumor types. The efficacy and safety of Vitrakvi® in TRK fusion cancer is studied in three multicentre open label and single arm phase I/II trials (LOXO-study, SCOUT-study and NAVIGATE-study), which is pooled into one analysis that hereon can be referred to as the Vitrakvi® trial. The pooled analysis of all 3 studies is the basis for the approved indication.

Vitrakvi® shows an ORR of 79-80% with a median DoR of 25.8-36.8 months. The effect of Vitrakvi® is seen regardless of tumor location or age. Median time to response is 1.8 months. Median OS is not reached. Patients show long-term efficacy. Further, some patients may discontinue treatment with Vitrakvi® due to pathological complete response after surgery. This is shown in pediatric patients, where Vitrakvi® allows pediatric patients to avoid disfiguring surgery, such as amputation. Thereby avoiding devastating and lifelong consequences.

To determine the effectiveness of drugs studied in a single arm trial, ESMO developed a Magnitude of Clinical Benefit Scale (MCBS) (Cherny 2017). Further studies may show if these patients can stay off treatment without the cancer coming back as potentially cured. MCBS includes several categories (Cherny 2017). The highest score is 3 for single-arm trials in orphan disease states or those with a high unmet need if the criteria below are fulfilled: an ORR of >60%, or a median PFS >6 months, or an ORR ≥20% to <60% and a DOR ≥9 months (Cherny 2017). Vitrakvi® has the highest score, score 3, based on ESMO evaluation score.

Considering the rarity of TRK fusion cancer and all evidence outlined, Vitrakvi® should be recommended as standard treatment in TRK fusion cancer.

4 Introduction

Vitrakvi® is an oral bioavailable and highly selective TRK inhibitor. The target for Vitrakvi® is the TRK family of proteins, inclusive TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively. It is the first cancer drug to be EMA approved in a histology independent indication.

Gene fusion events resulting from chromosomal rearrangements of the human genes NTRK1, NTRK2, and NTRK3 lead to the formation of oncogenic TRK fusion proteins. These oncogenic proteins are aberrantly expressed, drive kinase activity and subsequently activate downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion cancer. TRK fusion cancer provide a targetable oncogenic driver across multiple solid tumor histologies. Although rare, these pan-cancer kinase fusion events are known to drive tumorigenesis across the multitude of histologies in which they are present. All patients with TRK fusion cancers, no matter the afflicted solid organ, share the same disease mechanism (Stransky 2014, Lange 2018). NTRK gene fusions have been reported in both the pediatric and adult patient populations.

Current treatment modalities for patients with a locally advanced, metastatic tumor without a satisfactory anti-tumoral treatment option is mainly chemotherapy (doxorubicin). There are currently no approved specific targeted therapies for patients with TRK fusion cancer, nor are there any European national consensus guidelines or literature references with recommendations for the clinical management of patients with TRK fusion cancer. However, Vitrakvi® shows a transformative efficacy with favourable safety profile across tumor types. Patients, where Vitrakvi® indication applies, receive today BSC chemotherapy which is represented by doxorubicin in the current application.

The efficacy and safety of Vitrakvi® in TRK fusion cancer is studied in three multicentre open label and single arm phase I/II trials (LOXO-study, SCOUT-study and NAVIGATE-study), which is pooled into one analysis that hereon can be referred to as the Vitrakvi® trial. The pooled analysis of all 3 studies is the basis for the approved indication. The primary endpoint for efficacy analyses is Overall Response Rate (ORR). Tumor responses are assessed using RECIST v1.1 criteria according to investigator assessment (INV). Duration of response (DOR), safety, overall survival (OS) and progression-free survival (PFS) are included as secondary endpoints. Quality of life (QoL) is included as an explorative endpoint.

In summary, the indication is pan-tumor agnostic in a rare cancer based on data which demonstrates durable efficacy across tumor types. The data will be presented in detail in the coming sections. The common denominator for all tumors is the detection of NTRK gene fusions. Moreover, all patients included in Vitrakvi® trials have a locally advanced or metastatic solid tumor. They have previously received standard or later-line chemotherapies and have no other satisfactory treatment options available. Thus, Vitrakvi® is aimed at a very specific population with a high unmet medical need.

This document follows the application form developed by the Medicine Council (version 2).

5 Literature search

Method

A literature search is performed according to the protocol developed by the Medicine Council for the evaluation of clinical added value of Vitrakvi® (larotrectinib) for the treatment of patients with TRK fusion cancer.

An electronic search is run in PubMed (MEDLINE) and Cochrane Central on the 17th-19th March 2020. The search includes all the search terms described in the protocol including different spelling and synonyms. Articles that studies the outlined PICO-factors in the protocol are searched. The search strategy is outlined in Appendix 1.

Titles and abstracts are reviewed according to the inclusion criteria outlined in Table 3 below. Articles that meet the inclusion criteria are included for full-text reading. In case the abstract is not available or if the relevance is unclear, then the articles are included for full-text reading. Articles that are excluded after full-text reading are listed together with the reasons for exclusion in Appendix 1. A flow diagram showing the number of references identified and the number of included and excluded references is also found in Appendix 1.

Table 3. In and exclusion criteria for the literature review

	Inclusion criteria	Exclusion criteria
Population	TRK fusion cancer	
Intervention	Vitrakvi® (larotrectinib)	
Comparator(s)	Best Supportive Care (BSC)	No restrictions
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Overall Response Rate (ORR) • Quality of Life (QoL) • Adverse events	
Study design	Randomized control trials (phase I-III)*, observational studies	Non-interventional studies Case reports
Language restriction	English	
Publication dates	No restrictions	

*In the case that phase ll-III studies are available the respective phase I study is not included.

In addition, EMA's public assessment report (EPAR) is consulted as well as the product resume for Vitrakvi®.

Results

A literature search is done in PubMed (Medline) and Cochrane on Vitrakvi® and placebo/BSC. The search results in 92 articles, of which 10 are relevant for full-text reading. Three articles meet the inclusion criteria (see appendix 1 for an overview) (Drilon et al 2018, Laetsch et al 2018 and DuBois et al 2018).

Two (Laetsch et al 2018 and DuBois et al 2018) of the three articles that meet the inclusion criteria capture subgroup results that are also captured by Drilon et al (2018), which is the main-study. Hence, we will shortly summarize the three articles in section 5.1. and in section 5.2. which outlines the main study.

In addition to the literature review we also include a recent publication on interim-results by Hong et al (2020). Hence overall the literature search leads to four articles.

5.1 Relevant studies

The literature review is covered by four articles regarding the Vitrakvi® trial. A short review of the publications is given in Table 4. All publications are from one and the same trial. Two of the publications are from interim

analysis, data cut-off at different point of time in line with the ongoing trial. Two of the publications are subgroup analysis on pediatric patients.

Drilon et al (2018) presents the first interim-results from the data cut-off Feb 2017 and Hong et al (2020) presents interim-results from Feb 2019. Laetsch et al (2018) and DuBois et al (2018) present data from subgroup analysis on pediatric patients from published results by Drilon et al (2018), mentioned above.

In section 5.2 we outline the Vitrakvi® studies characteristics and design whereas in section 7 we present results. Please see table 4 for brief review of published articles from the Vitrakvi® trial. Results published previously are shortly summarized in appendix 2.

Table 4 Relevant studies included in the assessment

Reference (title, first author, year, journal)	Trial name (NCT number)	Dates of study (start and expected completion date)	Relevant for clinical question*/NOTE
Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children, **Drilon et al 2018**, New England Journal of Medicine	• LOXO-TRK-14001 (NCT-02122913): adult, phase-I • SCOUT LOXO-TRK-15003 (NCT-02637687): children, phase-I/II • NAVIGATE LOXO-TRK-15002 (NCT-02576431): adult and adolescent, phase II	• NCT-02122913: Start in May, 2014 & Study Completion Date in March, 2021 • NCT-02637687: Start in December 2015 & Study Completion Date in August 2027 • NCT-02576431: Start in September 2015 & Study Completion Date in September 2025	This article describes the first results for the pooled efficacy analysis for Vitrakvi®. Data cut-off is February 2017.
Larotrectinib for pediatric solid tumors harbouring NTRK gene fusions: phase 1, **Laetsch et al 2018**, The Lancet	• SCOUT LOXO-TRK-15003 (NCT-02637687): children, phase-I/II	• NCT-02637687: Start in December 2015 & Study Completion Date in August 2027	This article describes the efficacy and safety of Vitrakvi® for pediatric patients only. The article is a sub-analysis that is also covered in Drilon et al 2018.
The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas, **DuBois et al 2018**, Cancer, 2018	• SCOUT LOXO-TRK-15003 (NCT-02637687): children, phase-I/II	• NCT-02637687: Start in December 2015 & Study Completion Date in August 2027	This article describes the efficacy and safety of Vitrakvi® for pediatric patients with sarcoma only. The article is a sub-analysis that is also covered in Drilon et al 2018.
Larotrectinib in patients with TRK fusion-positive solid tumors: a pooled analysis of three phase 1/2 clinical trials, **Hong et al 2020**, The Lancet	• LOXO-TRK-14001 (NCT-02122913): adult, phase-I • SCOUT LOXO-TRK-15003 (NCT-02637687): children, phase-I/II • NAVIGATE LOXO-TRK-15002 (NCT-02576431): adult and children, phase II	• NCT-02122913: Start in May, 2014 & Study Completion Date in March, 2021 • NCT-02637687: Start in December 2015 & Study Completion Date in August 2027 • NCT-02576431: Start in September 2015 & Study Completion Date in September 2025	This article is an extended study for Drilon et al. 2018 and describes the interim results for the pooled efficacy analysis for Vitrakvi®. Data cut-off is February 2019.

5.2 Main characteristics of included studies

The clinical program that evaluates the clinical effectiveness and safety of Vitrakvi® in adult and pediatric patients with TRK fusion cancer is made up of three multi-center open label, phase I/II and single arm trials. Two of these studies are still recruiting patients.

The studies have been ongoing at the time of market approval and are still ongoing:

- LOXO-study TRK-14001 (NCT-02122913): adults (recruitment ended) phase-I
- SCOUT-study LOXO-TRK-15003 (NCT-02637687): pediatric patients, phase-I/II (SCOUT)
- NAVIGATE-study LOXO-TRK-15002 (NCT-02576431): adult and adolescent, phase II (NAVIGATE)

The LOXO study and the phase-I enrolment of the SCOUT study are open to any patient with advanced solid tumors. This differs from the study design of the phase-II enrolment of the SCOUT study and the NAVIGATE study, which includes only patients with tumors harbouring a documented NTRK gene fusion i.e. patients with TRK fusion cancer.

Patients included have a locally advanced or metastatic solid tumor who have previously received standard therapy, have an ECOG PS of 0 to 2, and have adequate major organ function. The common in- and exclusion criteria for the Vitrakvi® trial are given in Table 5. The primary endpoint for efficacy analyses is ORR. Tumor responses are assessed using RECIST v1.1 criteria according to investigator assessment (INV). Duration of response (DOR), safety, overall survival (OS) and progression-free survival (PFS) are included as secondary endpoints. QoL is included as explorative endpoint measured with EORTC QLQC-30 (adults) and PedsQL (pediatrics).

Treatment is given until disease progression or until unacceptable toxicity occur. Patients (adults, adolescents, and children) with a BSA ≥1 m^2 are given Vitrakvi® 100 mg twice daily. Patients that experience an adverse event can reduce their dose and continue with Vitrakvi®. Children with a BSA <1 m^2 are administered Vitrakvi® 100 mg/m^2 orally twice daily. Note that patient with primary CNS are analysed separately, see section 8.2.

Tabell 5. In- and exclusions criteria for the Vitrakvi®-trial

Inclusion criteria	Exclusion criteria
Patients with a locally advanced, non-primary CNS or metastatic evaluable solid tumor with a confirmed NTRK gene fusion who have previously received standard therapy, have an ECOG PS of 0 to 3, and have adequate major organ function are eligible for enrolment.	Patients who receive previous treatment with kinase inhibitors with anti-TRK activity are excluded. Note: This is an early amendment to the phase 2 study and 1 patient is enrolled prior to the amendment who receive such therapy (Bayer EMA SCE 2018).

The results are integrated into one analysis leading to efficacy and safety data for pediatric and adult patients with TRK fusion cancer. The consistency of treatment response, safety, age groups and across common eligibility criteria in these rare cancers permits the pooling of interim data in support of global regulatory submissions. **The primary data-set (PAS)** of 55 pediatric and adult patients, with a data cut-off performed in **July 2017** has been the base for FDA approval (Drilon et al 2018). The Extension of the primary data-set from a data cut-off performed in July 2018, which includes 93 pediatric and adult patients with solid tumors (38 additional patients) and 9 additional primary CNS tumor, has been the base for EMA approval of Vitrakvi® (SPC 2019). As mentioned, patients are continuously followed with **July 2019 being the latest data cut-off at this date**. The data-sets include all patients with a follow-up time equal or longer than 6 months.

Pooled analysis from data cut-off in July 2019 is used for the purpose of this application. This data is referred onwards as the Vitrakvi® trial. There are two main data-sets:

- The pooled analysis of **Primary data-set** including 55 TRK fusion cancer patients with a data cut-off performed in **July 2019** is called **Primary data-set July 2019 (PAS-July 2019)** (Data on file Bayer**).**
- **The extended data-set** includes patients from PAS-data (n=55) and all other patients recruited overtime until **data cut-off July 2019**. This is referred to as **extended Primary Analysis Set (ePAS-July 2019)** (n=164) (Data on file Bayer). This is the full data-set available to date for Vitrakvi® trial.

These data-sets are data on file. However, study design, study population and method are similar to published data by Drilon et al 2018 and Hong et al 2020. Table 6 below provides a short overview of the data-sets.

The main reason for focusing on the most recent data cut-off, rather than earlier published data cut-offs, is to provide efficacy data based on the longest possible follow-up time and the largest data set. This is in line with the protocol recommendation by the Medicine Council. Moreover, a later data cut-off with a long-term efficacy data is required to show the added clinical value provided by Vitrakvi® and to assess the economic implication over a life-time horizon. Hence, the two main data-sets represented by the PAS-data (data cut-off July 2019) and ePAS-data (data cut-off July 2019) are used for presenting results and comparisons in the current application.

Table 6.Overview data-sets

Pooled analysis data-set	Interim analysis and Data cut-off	Description	N	Supporting Documents
Primary Analysis Set (PAS)	Latest data cut-off: July 2019	The first patients enrolled in the Vitrakvi®-trial and **the data-set with the longest median follow-up time**	55	Drilon et al 2018; Data on file but soon to be available in Bayer SPC 2020
Extended Primary Analysis Set (ePAS)	ePAS2 has a data cut-off in July 2018	Patients from the PAS data-set and patients included before cut-off July 2018 with TRK fusion cancer	93	EPAR 2019; Bayer SPC 2018
	ePAS3 has a data cut-off in Feb 2019	Patients from the PAS data-set and included before cut-off Feb 2019 with TRK fusion cancer	153*	Hong et al 2020
	ePAS4 has a data cut-off in July 2019	Patients from the PAS data-set and included before cut-off July 2019 with TRK fusion cancer and a follow-up time longer than 6 months. **The data-set with the largest number of patients.**	164	Data on file but soon to be available in Bayer SPC 2020

* 153 of 159 patients included in the integrated dataset have been evaluable for efficacy. Six patients were not evaluable due to post-baseline assessments being incomplete

All identified publications represent pooled analysis for interim-results at different point of time. ePAS4 is the data-set used in this evaluation and for simplification referred to as ePAS (data cut-off July 2019).

Baseline characteristics are similar in the PAS and ePAS-data as Table 7 shows.

Table 7. Overview on baseline characteristics per data-set

Dataset	PAS	ePAS	PAS Adults only	ePAS Adults only	PAS Pediatrics only	ePAS Pediatrics only
Data cut-off	July 2019	July 2019	July 2019	July 2019	July 2019	July 2019
Total patient population	55	164	43	109	12	55
Median follow-up time. months	31.8	14.5	31.2	14.3	32.8	15.3
Median age, years	45 (range 0.3-76)	42 (0.05-84)	57 (24-76)	56 (19-84)	1.8 (0.33-12)	1.2 (0.05-14)
Number of children, %	21.8	34.2	0	0	100	100
Number of women, %	47	52	47	0.53	50	47
Performance status, %	ECOG	ECOG	ECOG	92	ECOG	ECOG
0 or 1	93.0	86.0	93.0	84.4	92.0	91.0
>=2	7.0	14.0	7.0	15.6	8.0	9.0
≥1 earlier treatment (%)	80	78	79.1	80.7	83.0	74.0
Primary tumor location	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS)	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS), Hepatic, Bone sarcoma, Congenital mesoblastic nephroma, prostate	Appendix, Breast, Cholangiocarcinoma, Colon, GIST, Lung, Melanoma, Pancreas, Salivary gland, Soft tissue sarcoma and Thyroid	Appendix, Bone sarcoma, Breast, Cancer of unknown primary, Cholangiocarcinoma, Colon, GIST, Hepatic, Lung, Melanoma, Prostate, Salivary gland, Soft tissue sarcoma, Tyroid	Infantile fibrosarcoma, soft tissue sarcoma	Melanoma, Soft tissue sarcoma, IFS, Congenital mesoblastic nephroma, Thyroid

6 The comparator

Clinical practice for patients with a locally advanced, metastatic tumor without a satisfactory anti-tumoral treatment option is BSC in the form of antitumoral treatment. This means last line chemotherapy represented by doxorubicin.

Doxorubicin can be used as a representative for other chemo therapies, both in mono and in combination since there is no evidence supporting a difference in effect between different chemotherapies or combinations. Chemotherapy (represented by doxorubicin) is the anti-tumoral treatment used when there are no other alternatives left for these patients. This treatment modality is in line with the Vitrakvi® protocol developed by the Medicine Council.

The effect of Vitrakvi® is studied in a single arm trial because,

- TRK fusion cancer is a rare disease. If patients would have been randomized to two treatment arms (one active arm being Vitrakvi® and a comparator arm being doxorubicin) this would have resulted in

poor statistical power. A randomized trial would lead to either a low number of patients in each arm or an extremely long period of inclusion and follow-up time.

- A single arm trial design avoids confounded OS results due to expected cross over since Vitrakvi® is a precision medicine that if compared to doxorubicin would show significant OS and leaving patients in the comparator arm would be unethical.

In order to bridge possible uncertainties combined with a single arm trial, a comparator arm representing the effect of antitumoral treatment such as treatment with doxorubicin is established within the Vitrakvi® trial using the primary data set in the following way:

1. The underlining assumption is that the efficacy of non-responding patients from the Vitrakvi® trial represent the same outcome as if they are treated with doxorubicin. Non-responding patients are defined as patients with stable disease and progressors but also an approximation of patients with CR and PR with a DoR of less than 24 months. Please see section 6.1. for a detailed explanation.

2. Hence, the efficacy of all Vitrakvi® patients is compared to the efficacy of Vitrakvi® non-responders, which we can call a Proxy-control arm BSC. Note that the Proxy-control arm BSC includes mainly adult patients (90%).

This proxy-control arm is backed-up trough validation by two other sources: 1) the doxorubicin arm and 2) the Growth Modulation Index (GMI)-curve (intra-patient comparison). Both the doxorubicin-curve and the GMI-curve lie very close to our proxy-control-arm, which shows that our proxy-control-arm are by high likelihood representing the effect a real control arm would have shown.

The GMI is an intra-patient comparison, where PFS on a patient's previous treatment is compared to the PFS of the Vitrakvi® treatment (Von Hoff et al 1998). Here each patient is their own control minimizing possible confounders due to difference in baseline characteristics between two treatment arms.

This GMI method gives a valuable insight by estimating the different in effect between Vitrakvi® and previous treatment. This approach is similar to having a historic treatment of TRK fusion cancer before TRK inhibitors, such as Vitrakvi®, have been available. Therefore, the GMI-index curve is as close as can be to a real comparator arm.

Von Hoff that proposes using intra-patient comparison values the GMI as a way to detect whether a new agent is having a modulating effect on tumor growth (Von Hoff 1998). Using a patient as his/her own control, the approach suggests that time to progression tends to become shorter with successive lines of therapy. Given the natural history, one would expect time to progression to be shorter on the next treatment compared to the previous treatment. If a new agent has an anti-tumor effect, it will change the natural history of the disease so meaning that the time to progression is longer for the new (later given) treatment than the previous treatment.

This analysis is performed on the 164 patients (ePAS, data cut-off July 2019). The GMI analysis is run on the ePAS data (data cut-off July 2019) and includes patients who have at least one prior therapy in any setting (122 patients). The median GMI, which is a sign of clinical activity defined when the GMI value is ≥1.33 (Von Hoff 1998), is 3.35 (range: 0.00 - 337.0) in the population with at least 1 prior therapy in any setting (n=122). The HR is 0.204 (95% CI: 0.144-0.288). Von Hoff outlines that “the threshold of 1.33 is arbitrary but considered excellent and unexpected for second-line therapy” and by extension to any new line of therapy. Most importantly however the GMI-curve (presenting PFS) shows a similar effect as the PFS curve shown for the

proxy-control arm BSC, which often in reality is doxorubicin, (see Judson et al 2014). Results have recently been presented at ASCO (2020). The validation is shown in section 6.3.

6.1 The comparator arm: Proxy-control arm BSC

As mentioned, the Vitrakvi® study is a single arm trial because a randomized trial in a rare cancer types such as TRK fusion cancer would either result in too little power or would have to last over several years for inclusion and even longer to show significant OS results.

- To illustrate the effect of non-responders the OS and PFS results for patients achieving stable (SD) and progressive (PD) are shown. These patients have been treated with Vitrakvi® but have not achieved response in the form of CR or PR. Patients receiving chemotherapy are not expected to achieve treatment outcomes similar to those treated with precision drugs. Thus, non-responders from the Vitrakvi® study can serve as a control arm in the study as they achieve efficacy similar to doxorubicin**.** We thus call non-responders from the Vitrakvi® study a Proxy-control arm BSC, which in reality often would be represented by doxorubicin.

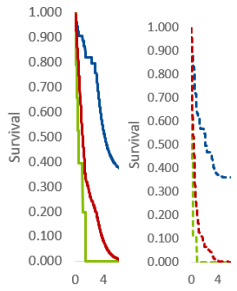
  The proxy-control arm does also illustrate the effect for patients with CR and PR with DoR less than 24 months. These patients are physically not represented in the proxy-control arm but the proxy-control arm can rather be seen as a possible approximation.

  The patients with CR or PR with DoR less than 24 months might in a future follow-up analysis turn out to be long-term survivors. Currently the majority of these patients have censored events as they are both progression free and alive. As patients are censored it is not necessary that these patients are physically represented in the curve. The approximation – to have only patients with SD and PD physically placed in the proxy-control-arm – is estimated to implicate that a true comparator curve containing also censored patients with CR or PR with a DoR less than 24 months would lie somewhere in between the current proxy-control-arm and the doxorubicin-arm in red in the figure below.

  The Proxy-control arm BSC has been validated with long-term doxorubicin data from Judson 2014. This minimizes major uncertainties that are usually imposed on unarmed studies. In Figure 1 below we can see that the Doxorubicin OS curve overlaps that of the Proxy-control arm BSC almost perfectly during the course of the study demonstrating that the **Proxy-control arm BSC** behaves like a genuine control arm.

The treatment effect with Vitrakvi® in pediatric patients is compared to the Proxy-control arm BSC (consistent of both adult and pediatric patients) and doxorubicin (Judson et al 2014). Almost all pediatric patients respond to treatment with Vitrakvi®, which is why the non-responders group for pediatric patients is too small to create their own Proxy-control arm BSC (0% and 10% in the PAS and ePAS data respectively). The adult curve for doxorubicin and the Proxy-control arm BSC are applicable to pediatric patients who present with locally advanced unresectable disease, where Vitrakvi® is indicated. Pediatric patients are, generally speaking, doing very well on first-line chemotherapy treatment, but pediatric patients who have received several lines of treatment, and/or for whom no other suitable treatment is available, are deteriorating quickly. Hence, Bayer use the Proxy-control arm BSC for the entire patient population as a comparison arm among pediatric patients. In the cost analysis we have also run some subgroup analysis with alternative treatment options being mutilating surgery for pediatric patients with no treatment alternatives and comparison to pediatric patients with relapsed or progressed solid tumors.

Figur 1. KM-graph for doxorubicin (red curve) (Judson et al 2014) validating the Proxy-control arm BSC (green line): the left figure shows the OS and the right figure shows PFS. The blue line shows the effect for Vitrakvi®



Source: Vitrakvi® trial data, Judson et al 2014 and cost-minimization model for Vitrakvi® compared to BSC

Prognostic characteristics are similar for patients in the Vitrakvi® arm and patients in the proxy-control arm. As seen in the table below the patients in the Vitrakvi® trial (PAS and ePAS4) have similar baseline characteristics as patients in the proxy control arm.

Table 8. Baseline characteristics

Analysis set	Vitrakvi® PAS	Proxy control arm PAS	Vitrakvi® ePAS4	Proxy control arm ePAS4
Data-cut	July 2019	Non-responders from PAS-data (evaluated as SD and PD)	July 2019	Non-responders from PAS-data (evaluated as SD and PD)[1]
N	55	11	164	30
Age, years, median	45 (range 0.3-76)	43 (24-74)	42 (0.05-84)	50 (1.6-77)
Pediatric, %	21.8	0	34.2	10
Female, %	47	73	52	60
Performance status, %	ECOG	ECOG	ECOG	ECOG
0 or 1	93	82	86	77
>=2	7	18	29	23
>=1 previous systemic therapy (%)	80	91	78	87

More patients in the proxy-control-arm have undergone more than 1 previous systemic therapy.

Nevertheless, when breaking the variable down to number of patients with 1, 2 or more than 3 previous therapies the baseline characteristics become nearly similar between the Vitrakvi® arm and proxy-control arm, see Table 9 below.

There are more patients with no previous line of therapy in the Vitrakvi®arm than in the proxy-control-arm (doxorubicin), which can be explained due to the percentile difference in number of pediatric patients in the respective treatment arm.

[1] In the ePAS data-set 4 patients have been defined as non-determinable/non-evaluable one example for this classification is that a patient missed post-baseline assessments. Those 4 patients are included in the OS and PFS curve for the Proxy-control arm BSC but there are not included in the calculation of absolute and relative difference for the respective outcomes for example OS-rate at 24 months. These patients do however progress during an interval of 0-1 months which is their impact on the effect is highly limited. For informational purposes baseline characteristics for these four patients are shared with MR, see file baseline characteristics for patients that are non-determinable/non-evaluable.

- Firstly, there are few pediatric patients in the comparator arm since pediatric patients have a high response rate to Vitrakvi®. Note, the ORR for pediatric patients treated with Vitrakvi® have an ORR of 95-100%.

- Secondly, Vitrakvi® is indicated when there is no treatment alternative available for patients with metastatic and local advanced disease where surgical resection is not possible. In order to avoid sever resections in pediatric patients such as amputation, treatment with Vitrakvi® is introduced and hence might be the first treatment option a pediatric patient receives. As we see in Table 7 above some pediatric patients are as young as 4 months (=0.3 years) in the PAS data (July 2019).

Table 9. Number of previous line of therapies between treatment arms.

Number of Prior Systemic Regimens	Vitrakvi® PAS (n=55)	Proxy control arm (n=11) Patients with non-respons from PAS	Vitrakvi® EPAS4 (n=164)	Proxy control arm (n=30) Patients with non-respons from ePAS4
0	11 (20%)	1 (9%)	36 (22%)	4 (13%)
1	16 (29%)	3 (27%)	50 (30%)	13 (43%)
2	9 (16%)	3 (27%)	34 (21%)	5 (17%)
3 or more	19 (35%)	4 (36%)	44 (27%)	8 (27%)

The Proxy-control-arm is further validated by means of the doxorubicin-arm, which lies a bit higher than the Proxy-control-arm. Thus, a comparison versus doxorubicin is a conservative comparison, both from a relative effect perspective, and from a health economic perspective as well as a budget impact perspective:

- The curve closest to our Vitrakvi® arm produce the smallest "area under the curve" between the Vitrakvi® arm and the comparator arm
- Doxorubicin is the comparator lying closest to our Vitrakvi®arm – and thus produces the smallest area under the curve from all perspectives mentioned

6.2 Doxorubicin as a validation of BSC in terms of chemotherapy

Doxorubicin is used in a wide range of histologies and is considered a relatively efficacious and safe therapy. Further soft-tissue sarcoma (STS) is the most frequent tumor histology in the Vitrakvi® trial.

In the literature review that follows the search strategy outlined in appendix 2 of the MR protocol, Judson et al (2014) is identified as a source to validate and represent the efficacy and safety of BSC in terms of chemotherapy.

Judson et al investigates the efficacy and safety of doxorubicin in locally advanced or metastatic STS (Judson et al 2014). Furthermore, Judson et al, presenting the long-term efficacy for doxorubicin, confirms the relevance of the article. A short overview on the literature search and description of this article is given in the appendix 3. Baseline characteristics are shown below in table 10.

Table 10. Doxorubicin baseline characteristics

Publication	Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial (Judson et al 2014)
Population	Adult patients with high-grade soft-tissue sarcoma with unresectable or metastatic disease progression within 6 weeks before treatment
N	228
Follow-up, months, median	56.4
Age, years, median	48 (range 18-60)
Pediatric, %	0

Female, %	55
Performance status, %	WHO
0 or 1	100
>=2	<1
At least one previous systemic therapy (%)	NR
mOS, months	12.8 (CI 10.5–14.3)
mPFS, months	4.6 (CI 2.9–5.6)
Site of active disease	Different soft tissue sarcoma types: undifferentiated pleomorphic sarcoma, myxoid or round cell liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, synovial sarcoma, myxofibrosarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, epithelioid sarcoma, unclassified high-grade sarcoma (not otherwise specified))

6.3 Validation of the control arm

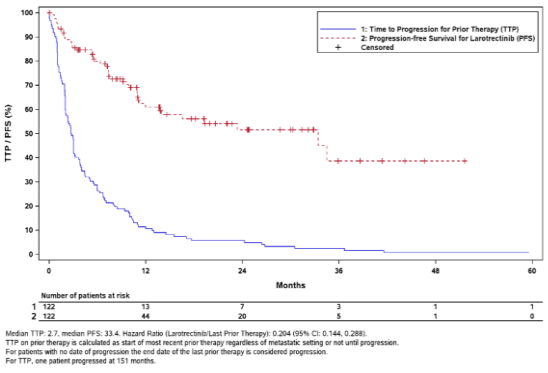
Standard of care for patients today, before Vitrakvi® on the market, where there exists no other alternative is doxorubicin (representing all other chemo therapies). The doxorubicin arm validates both the intra-patient comparison as well as the proxy-control-arm.

Comparing the PFS-curves for the proxy-control-arm and the GMI-arm in Figure 2 and 3 below we see that the hypothesis if patients in the proxy-control arm really match the GMI-arm is proven and that the proxy-control-arm can be viewed as a realistic control arm.

In Figure 2, the red KM curve shows the effect among patients treated with Vitrakvi® according to IRC (Independent Review Committee). The blue curve shows time to progression for the same patients on the previous treatment. If we compare the blue curve in Figure 2 versus the proxy-control arm and doxorubicin arm in Figure 3, we see that those are very similar:

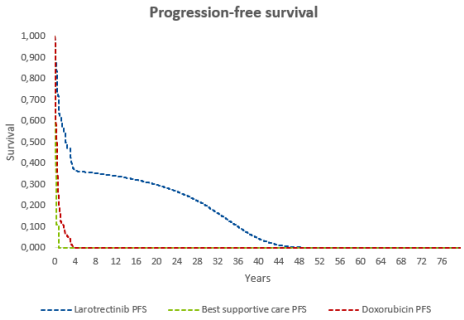
- At 12 months follow up: In all arms the probability of being progression free is between 12% to 15%
- At 24 months follow up: In all arms the probability of being progression free is between 8% to 10%
- At 48 months follow up: It is important to note that some patients are censored, namely those patients with CR and PR who has a shorter follow time than 24 months. Those patients can turn out to be long term survivors at later data cuts. For now, it thus looks like the probability in all arms of being progression free is 0%

Figure 2. Kaplan Meier – Time to progression on previous treatment (blue) and PFS for Vitrakvi® (red)



Median TTP: 2.7, median PFS: 33.4, Hazard Ratio (Larotrectinib/Last Prior Therapy): 0.204 (95% CI: 0.144, 0.288).
TTP on prior therapy is calculated as start of most recent prior therapy regardless of metastatic setting or not until progression.
For patients with no date of progression the end date of the last prior therapy is considered progression.
For TTP, one patient progressed at 151 months.

Figure 3. Extrapolated weighted PFS curve for TRK-fusion cancer patients treated with Vitrakvi® (blue), proxy-control arm and doxorubicin (green and red)



The doxorubicin-curve lies slightly above the proxy-control-arm. Thus, a comparison versus doxorubicin is a conservative comparison, both from a relative effect perspective, and from a health economic perspective:

- The curve closest to our Vitrakvi® arm produce the smallest "area under the curve" between the Vitrakvi-arm and the comparator arm

- Doxorubicin is the comparator lying closest to our Vitrakvi® arm – and thus produces the smallest area under the curve from all perspectives mentioned.

7 The added clinical value of Vitrakvi®

In section 7.1, we present the results from the clinical trial for the total study population of the Vitrakvi® trial, with PAS-data (July 2019) and ePAS-data (July 2019) (section 7.1.1), i.e. pooled analysis from the latest data cut-off. Pediatric and adult patients are also presented separately according to the requests of the protocol by Medical Council (section 7.1.2 and 7.1.3). In section 7.1.4., the comparative results are shown per outcome for both the overall patient population and pediatric and adult patients separately.

7.1 The added clinical value of Vitrakvi® in patients with TRK-fusion cancer

As outlined above all four publications found in the literature review are based on the Vitrakvi® trial. Main study characteristics and method are outlined in section 5.2.

7.1.1 Efficacy for Vitrakvi® in the overall patient population with TRK-fusion cancer

The first data-set with the longest follow-up time is represented by PAS-data, with data cut-off in July 2019.

The PAS-data consists of 55 pediatric and adult patients. Patients are included during the period of March 2015 until February 2017. Median age is 52 years ranging from the age of 3.6 months up to 76 years. 22% are children. Please see section 5.2 for more detail of the patient characteristics.

All patients have a follow-up time longer than 24 months. The ORR is 80% (40 out of 55 patients), 24% achieve complete remission (CR) and 56% are at partial remission (PR). Median time to first response is 1.81 (1.68–1.87) months. Median DoR is 35.2 (KI 19.8-NE) months indicating long-term efficacy. Median PFS is 25.8 (CI: 9.9-NE) months at a median follow-up time of 31.4 months. Median OS is not reached. The OS-rate at 24-month is 82% (KI: 71-93%).

The largest data-set is represented by ePAS-data, with data cut-off in July 2019. ePAS-data consists of 164 pediatric and adult patients, of whom 55 patients are from the PAS-data. Patients are included during the period of March 2015 until February 2019. Median age is 42 years including children from 5-month-old up to 84 years old. 34% of the included patients are children. Please see section 5.2 for more detail of the patient characteristics. Patient characteristics are similar to PAS-data.

ORR is 79% (130 out of 164 patients) of whom 19.5% have achieved CR and 59.7% are at PR. Likewise the PAS-data, the median time to response is 1.84 (1.68–1.87) months. Median PFS is 36.8 (CI: 25.7-NE) months at a median follow-up time of 13.8 months, which is 11 months longer than in the PAS-data. Median OS is not reached.

In a previous data cut-off that has been published by Hong et al (2020), median OS has been reported being 44.4 months (CI: 36.5-NE) at a median follow-up of 13.9 months (ePAS-data data cut-off February 2019). This data-set is from a data cut-off February 2019 including 159 patients. However, the median OS is not reached

at the latest data cut-off. The reason for a previous data cut-off to report median OS is based the methodology of Kaplan-Meier (KM) survival analysis, where number at risk influence the probability over time. Please see Appendix 4 for a detailed explanation. Nevertheless, the consistency of all data-sets are shown in previous and current sections with similarities in PFS, DOR, median time to first response and ORR. Moreover, KM-graph of OS for PAS-data and ePAS-data show a consistent similarity. At a timepoint of ≥ 24 months the OS-rate is 82% (CI: 75–90%). Please see below, figure 4 and 5.

Figure 4. OS for the overall patient population (PAS-data, n=55)

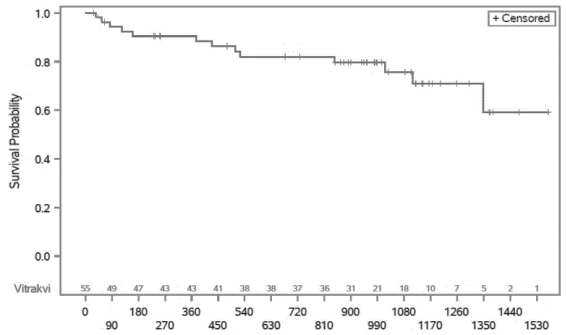
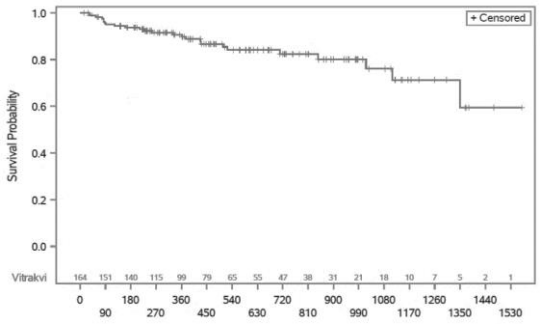


Figure 5. OS for the overall patient population (ePAS-data, n=164)



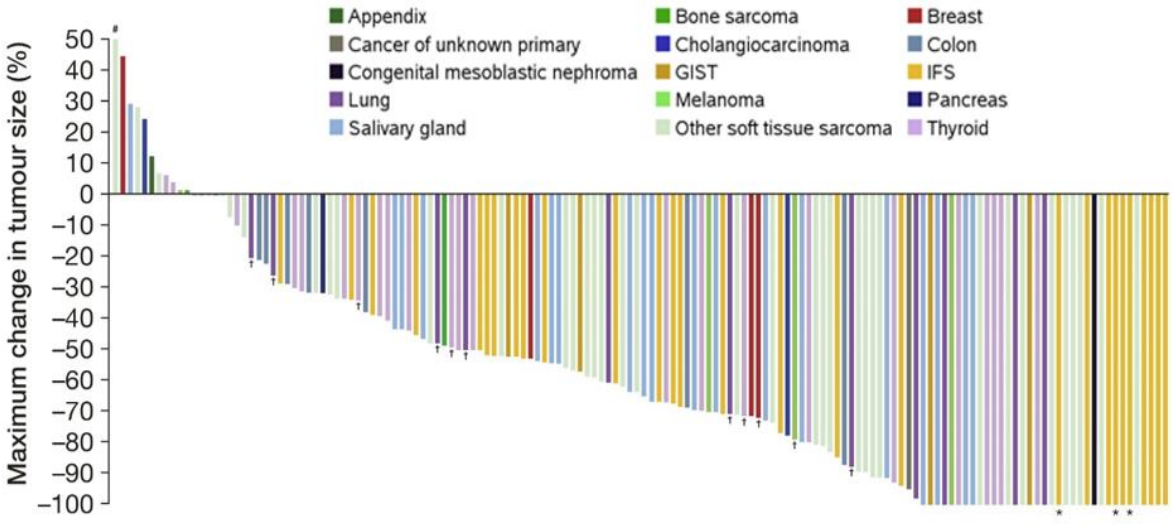
Data cut-off: July 2019

Vitrakvi® improves patient QoL and alleviates symptoms, evidenced by improvements in EORTC QLQC-30 (adults) and PedsQL (pediatrics). Results are shown per subgroup in section 7.1.2. and 7.1.3.

7.1.2 Efficacy for Vitrakvi® in adult patients with TRK-fusion cancer

Majority of patients included in the Vitrakvi® trial are adult patients with solid tumors. 43 and 109 adult patients with TRK fusion cancer are included in the PAS-data and ePAS-data (July 2019) respectively. Baseline characteristics are shown in Table 7 above. In the PAS data, ORR is 74.4%, of whom 25% achieve CR and 75% are at PR. Similar results are found in the ePAS July 19 data where ORR is 71.6% of whom 14.1% and 85.9% achieve CR and PR, respectively. The figure below shows the maximum change in tumor size according to primary diagnosis.

Figure 6. Waterfall plot for adult patients (Drilon et al 2020)



The median PFS for adult patient is 25.8 (15.2-NE) months. Median OS is not reached. At the ASCO conference results have been published for adult patients. In total the results include 116 patients of whom 109 patients are from the ePAS data-set with a follow-up time longer than 6 months and 7 patients that have a follow-up time shorter 6 months as they have been recruited between the previous and last data cut-off (Feb 2019 - July 2019). The KM-graph for OS is presented below showing the landmark OS at 12 months being 87% and at 24-months 76%.

Figure 7. PFS for the adult patient population treated with Vitrakvi® (Drilon et al 2020)

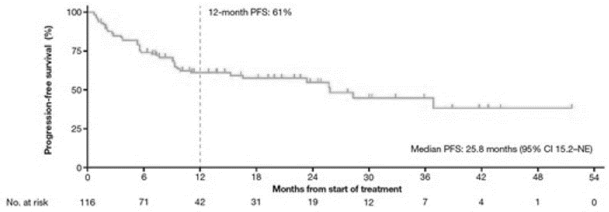
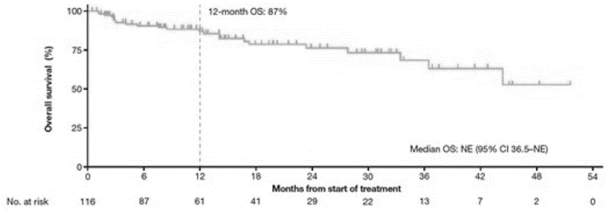


Figure 8. OS for the adult patient population treated with Vitrakvi® (Drilon et al 2020)



QoL in adult patients is reported for the ePAS-data (July 2019). QoL is measured with the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire Global Health Score (EORTC-QLQ-C30) in the Navigate study of the Vitrakvi® trial. 85 patients are reported at the baseline assessment and 74 have at least one postbaseline assessment. 59% of these patients have a best postbaseline score at or above (≥ 10 points) Minimum Important Difference (MID) improvement.

Table 11. EORTC QLC-C30

PRO Instrument	Domains	Score Range	Score Direction
EORTC QLQ-C30	5 functional scales: physical, role, cognitive, emotional, and social Global health status 3 symptom scales: fatigue, pain, and nausea and vomiting Additional single items assessing symptoms: dyspnea, loss of appetite, insomnia, constipation, and diarrhea Perceived financial impact of disease	All scales and single-item scores are standardized and range from 0 to 100	Functional scales and global health: higher is better; a positive change from baseline means improvement in functioning Symptoms scales and single items: lower is better; a negative change from baseline means improvement in symptoms Global health status MID: a change in score of 10 points or more (Cocks et al., 2012; Osoba et al., 1998)

7.1.3 Efficacy for Vitrakvi® in pediatric patients with TRK-fusion cancer

Vitrakvi® is effective for the overall patient population, but pediatric patients show an even greater ORR and greater survival probability. ORR is 95-100% for pediatric patients compared to 79-80% for all patients. In the PAS-data, OS rate at 24-month is 82% for the whole study population and 100% for pediatric patients only. Pediatric patients are defined as patients below 18 years old.

In the PAS-data (July 2019), 12 pediatric patients are included. The ORR for pediatric patients is 100% of whom 41.7% and 58.3% achieve CR and PR respectively. Neither median PFS nor median OS has been reached after a median follow-up time of 32.7 month, please see figure 9 and 10.

In PAS-data, 3 out of 12 have progressed. No death event has occurred. 3 out of 12 pediatric patients have curative surgery that lead to discontinuation of treatment with Vitrakvi®.

In the ePAS-data (July 2019), 55 pediatric patients are included. The ORR is 95%, 38.1% achieve CR and 61.9% are evaluated as PR. Similarly, to the PAS July-2019 data-set, neither median PFS nor median OS has been reached. In the ePAS-data, 2 out of 55 pediatric patients have died during the first year of follow-up. However, the OS-rate remains at 94% in the following years, please see Figure 11. Risk for progression at 12-month landmark is 82%.

Figure 9. OS for children (PAS-data, n=12)

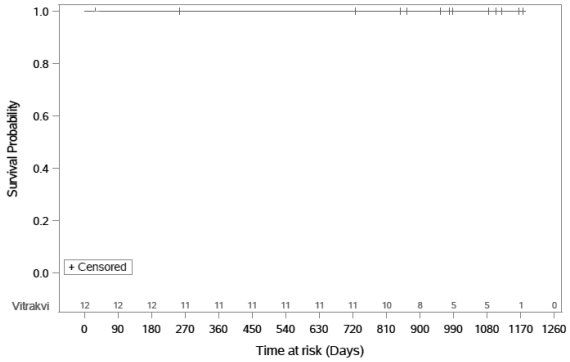


Figure 10. PFS for children (PAS-data, n=12)

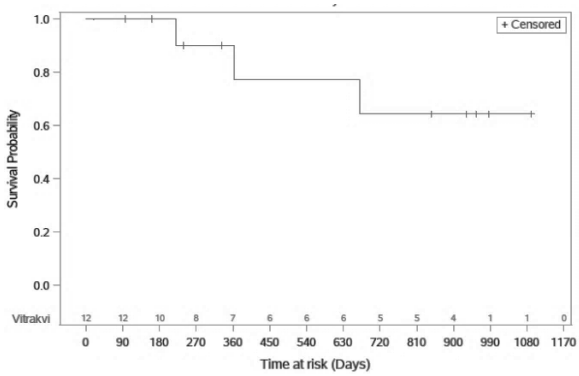


Figure 11. OS for children (ePAS-data, n=55)

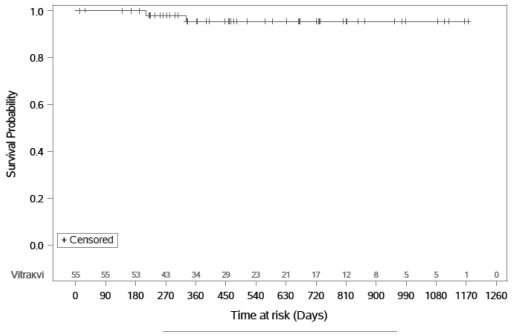
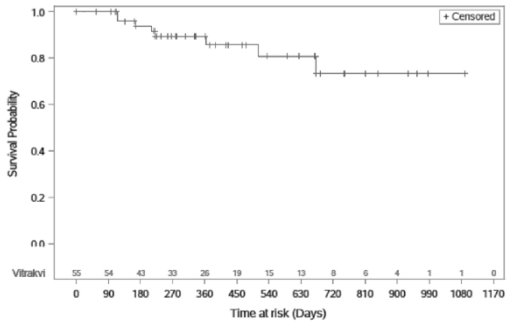


Figure 12. PFS for children (ePAS-data, n=164)



Data cut-off: July 2019

Quality of life is measured in pediatric patients with the Pediatric Quality of Life Inventory Total Score (PedsQL). Patients are from both the Navigate and SCOUT study of the Vitrakvi® trial assessed in ePAS July 2019. The methods for scores of the function domain and total scores with scales are given in table 12. A positive change from baseline indicates an improvement in the function. Data is available for 24 pediatric patients at baseline and during the trial duration. 79% of the patients have a best postbaseline score at or above MID improvement.

Table 12. PedsQL

PRO Instrument	Domains	Score Range	Score Direction
PedsQL infant (ages 1 to 24 months) PedsQL Generic Core Parent reported in toddlers (ages 2 to 4 years) Child and parent reported for young children (ages 5 to 7 years), children (ages 8 to 12 years), and teens (ages 13 to 18 years) Young adults and parent reported for young adults (ages 18 to 25)	4 functioning scales: physical, emotional, social, and cognitive 1 symptoms scale for infants: physical Physical score: the mean of physical functioning and physical symptoms for infants and the mean of physical functioning for children aged 2 years or more Psychosocial score: the mean of emotional, social, and cognitive items Total score: the mean of all items	All items are scored on a scale from 0 (never) to 4 (almost always) and reverse transformed: 0 = 100 (no problems), 1 = 75, 2 = 50, 3 = 25, 4 = 0 (serious problems)	All scales and scores: higher is better; a positive change from baseline means improvement in functioning Total score MID: a change in score of 4.5 points or more (Varni et al., 2007)

7.1.4 Comparative analyses for patients with TRK-fusion cancer per outcome and patient group

In this section we provide the results from the comparative analyses for each outcome outlined in the protocol. Results are structured according to outcome and presented per patient population (overall, adult and pediatric patients).

Data (PFS, OS, cPR) per tumor type and adult and pediatrics separately is currently not available for outcomes accept the ORR (both adult and pediatric patients combined). During a recent congress efficacy for Gastrointestinal cancer was shown for Vitrakvi®, which also combines results from different tumor types being colon, cholangiocarcinoma, pancreas, appendix, and hepatic (Berlin et al 2020) since patient numbers are already small and further post-hoc analysis of the data will lead to uncertainty. We do not find data per tumor type to be helpful as tumor site of origin (i.e. histology) is a minor variable in the pathologic description of the disease. For patients diagnosed with TRK-fusion cancer TRK-inhibitor-treatment, such as Vitrakvi®, has a mechanism of action which is independent of tumour site and entirely dependent on the presence/absence of NTRK-fusion proteins. Further we do not find that the subgroups are justified as there is no evidence of heterogeneity in treatment effect based on the totality of the trial data. As we later see in Figure 17 showing the waterfall plot of the maximum percentage change in tumor size according to primary diagnosis/ tumor type. As we see there is no cluster of a specific tumor type.

With the continuous recruitment of patients, data per tumor type increased both in patients and median follow-up time. During ESMO treatment specific results have been published for patients with TRK fusion cancer where the tumor is located in the lung or thyroid. The results are outlines in appendix 10.7.

OS-rate at 24-month landmark and median OS

In the protocol it is outlined that the expert group finds that the patient group at hand has an average low life expectancy and hence the expert group is interested in both OS-rate at 24 month and median OS. Vitrakvi® prolongs life. The OS-rate at 24-month is for the total study population 82% (71-93%) and 82% (75-90%) for PAS-data and ePAS-data respectively according to the latest data cut-off (see Figure 13-16). Results from an earlier cut-off published by Hong et al (2020) show similar results, where median OS has been documented due to the KM-method, please see appendix 4 for detailed information. Median OS is not reached for the Vitrakvi® arm neither for the overall patient population or when analysing results per age group (adults and pediatric patients separately) (Data cut-off July 2019).

Figure 13. OS for the overall patient population treated with Vitrakvi® (red) and BSC (blue) (PAS-data, n=55)

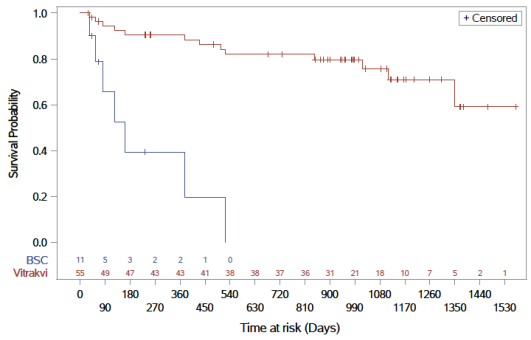


Figure 14. OS for the overall patient population treated with Vitrakvi® (red) and BSC (blue) (ePAS-data, n=164)

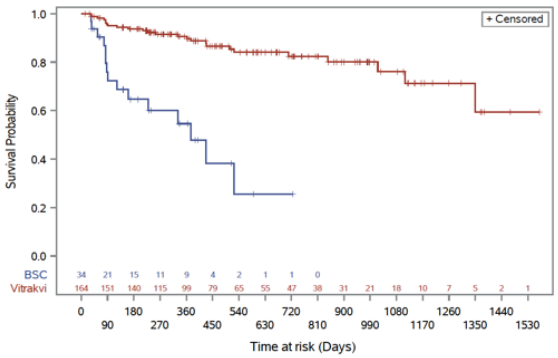


Figure 15. OS for pediatric patients for Vitrakvi® (red) and BSC (blue) (PAS-data, n=12)

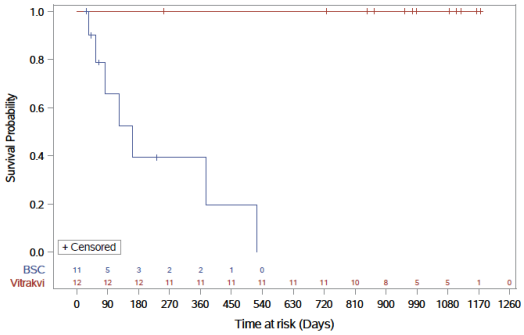
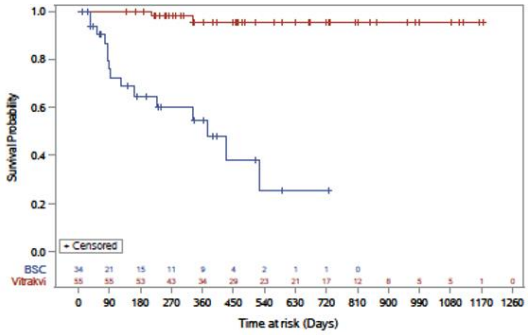


Figure 16. OS for pediatric patients for Vitrakvi® (red) and BSC (blue) (ePAS-data, n=55)



Data cut-off: July 2019

Table 13. OS-rate at 24 months

Population	Intervention	N	Results
Overall population (PAS)	Vitrakvi®	55	82% (71-93%)
	BSC	11	0%
Overall population (ePAS)	Vitrakvi®	164	82% (75-90%)
	BSC	30	Not reached*
Adult patients only (ePAS)	Vitrakvi®	109	76% (66-86%)
	BSC	30	Not reached*
Pediatric patients only (ePAS)	Vitrakvi®	55	95% (89-100%)
	BSC	30	Not reached*

*patients have an event or have been censored

As seen in Figures 13-16 and from Table 13. Patients in the Proxy-control arm BSC have either been censored or do not survive at 24-months (Bayer data on file 2020).

For doxorubicin the OS-rate is approximately 28% at 24-months (Judson et al 2014). For adults only, Vitrakvi® leads to an OS-rate at 24-months that is 76% and for pediatric patients to an OS-rate at 24-months of 95% (see Table 13). The absolute difference between Vitrakvi® and doxorubicin is 48% and 67% for adults and pediatrics respectively. The minimal clinical difference of 10% point is hence fulfilled, see the table below.

Based on the request from Medicine Council, Bayer has calculated the relative difference in OS-rate for Vitrakvi® (Data on file 2020) compared to doxorubicin (Judson et al 2014). Baseline characteristics are outlined in section 6.2.

In an unadjusted comparison the relative difference between Vitrakvi® and doxorubicin shows significant results for Vitrakvi® as seen in the table below. Pediatric patients treated with Vitrakvi® have an OS rate at 24 months of 95%. With lack of relevant studies regarding pediatric patients after first line treatment we assume that those pediatric patients might have a treatment response similar to results when treated with chemotherapy i.e. doxorubicin. If so the OS-rate at 24-months is more than three times greater for pediatric patients than for pediatric patients treated with doxorubicin, see the Table 14.

Table 14. OS-rate at 24-month for Vitrakvi® compared to doxorubicin

OS-rate at 24 months	Vitrakvi® ePAS, July 2019	Doxorubicin Judson et al 2014	Absolut Difference	Relative Difference HR (CI)
Overall patient population	82% (75 – 90%)	28% (22 – 34%)	54%	0.199 (0.143 - 0.278) p<0.0001
Adults only	76% (66 – 86%)	28% (22 – 34%)	48%	0.261 (0.185 - 0.368) p<0.0001

Pediatrics only	95% (89 – 100%)	28% (22 – 34%)	67%	0.061 (0.040 - 0.095) p<0.0001

Concerning median OS: For the overall patient population, median OS for the Proxy-control arm BSC is circa 13 months according to Figure 14 (from the ePAS-data, July 2019). For doxorubicin the median OS is 12.8 months (Judson et al 2014). Vitrakvi® has not reached median OS even at a median follow-up time of 32.5 and 15.8 months for PAS-data and ePAS-data (July 2019) respectively. Median OS has been reported before (Hong et al 2020) which is based on the Kaplan Meier methodology, see Appendix 4 for further information. This shows the survival gain achieved by treatment with Vitrakvi®. 23 deaths have occurred in the adult data, which includes 109 patients (ePAS-data July 2019). In the pediatric data, which included 55 patients, 2 death have occurred (ePAS-data July 2019).

Proportion of patients with pathological complete response or radical operation results

Vitrakvi® has shown data that will support a neoadjuvant treatment option. At data cut-off in July 2018, Vitrakvi® treatment demonstrates extensive tumor shrinking preventing radical surgery for pediatric sarcoma patients (DuBois et al 2018, Drilon et al 2018 and Laetsch et al 2018). Patients can thus avoid disfiguring amputation and permitting limb salvage and prevailing cure through surgery. In a later interim-analysis (data cut-off February 2019) seven patients discontinue Vitrakvi® treatment after surgery with curative intent (Hong et al 2020).

Results from the latest data cut-off show that 3 and 10 patients from the PAS-data and ePAS-data (July 2019) respectively have discontinued Vitrakvi® treatment in relation to surgery. In these cases, the tumor has been resected successfully allowing the discontinuation of Vitrakvi® treatment, shown below in table 15.

Table 15. Proportion of patients with pathological complete response or radical operation results

Proportion of patients with pathological complete response or radical operation results	**Overall population % (n)**		**Adult patients only % (n)**		**Pediatric patients only % (n)**	
	PAS-data (n=55)	ePAS-data (n=164)	PAS-data (n=43)	ePAS-data (n=109)	PAS-data (n=12)	ePAS-data (n=55)
	5.5 (3)	6.1 (10)	0(0)	0(0)	25 (3)	18.2 (10)

Data cut-off: July 2019

The proxy-control arm BSC does not have any patients documented that have curative surgery. The protocol outlines a medical added value can be defined if there is a difference between Vitrakvi® and BSC of at least 5%-point. As Table 15 shows Vitrakvi® meets this threshold. Current data can however only show curative surgery within the subpopulation children.

Quality of Life

Data on QoL is available only on aggregated level for ePAS-data (data cut-off July 2019). Results are published during ASCO (Kummar et al 2020)

The measurements of QoL and health utilities are exploratory objectives of the NAVIGATE and SCOUT studies, which are part of the Vitrakvi® trial i.e. pooled analysis.

In the NAVIGATE, exploratory objectives are to evaluate best changes from baseline in QoL and health utilities measures. The EORTC QLQ-C30, referred to as QLQ-C30 hereafter.

QoL for adult patients

The QLQ-C30 (version 3.0) is a well-validated instrument that assesses HRQoL in cancer patients. It includes 30 items and is composed of 5 functional scales: physical (5 items), emotional (4 items), role (2 items), cognitive (2 items), and social (2 items) functioning, as well as global health status (2 items). There are also 3 symptom scales measuring nausea and vomiting (2 items), fatigue (3 items), and pain (2 items) and 6 single

items assessing financial impact and various physical symptoms. Higher mean scores on these scales represent better functioning. A change of at least 10 points on the QLQ-C30 global health score is considered clinically meaningful (Cocks 2012, Osoba 1998).

QoL in adult patients is reported for the ePAS data-set (July 2019). Data is available for 74 patients as they have both responded at baseline and at least once post baseline. Comparison of QoL is shown by comparing the QoL both at average baseline vs average value of last visit for each individual. For comparison we also include the mean best observed value.

Table 16. Overview on QoL in adult patients measured with QLQ-C30

Label	N	Mean	Standard Deviation
Baseline QLQ-C30	74	64.9774775	23.4885465
Last QLQ-C30	74	70.6081081	19.5177286
Best QLQ-C30	74	82.4324324	15.1456380

Table 17 shows the frequency of change from baseline categories with the threshold for clinically meaningful change being defined as 10 points (Cocks 2012, Osoba 1998).

Table 17. Overview on QoL in adult patients measured with QLQ-C30

	Baseline vs last changes QLQ-C30	Baseline vs best changes QLQ-C30
Greater or equal 10, n (%)	27 (36.49)	44 (59.46)
Less than 10, n (%)	47 (63.51)	30 (40.54)

QoL for pediatric patients

The QoL in pediatric patients is measured with the PedsQL Core Module (version 4.0) in pediatric patients 2 years or older. The instrument uses child self-reporting as a generic core measure integrated into disease-specific modules to provide one assessment. The Generic Core Scales for children/adolescents consists of 23 items and 4 dimensions (physical, emotional, social, and school functioning). A 5-point Likert scale from 0 (never) to 4 (almost always) is reported for each item. The function scores were reverse transformed on a scale of 0 to 100, and higher scores indicate a better function. A positive change from baseline indicates an improvement in function.

Table 18. Overview on QoL in pediatric patients (2 years and older) measured with PedsQL

Label	N	Mean	Standard Deviation
Baseline PedsQL	24	68.1346331	21.4419100
Last PedsQL	24	82.9812684	18.8064152
Best PedsQL	24	88.8629109	14.5648676

When analysing the frequency of change from baseline categories, the majority reaches the threshold for clinically meaningful change being defined as 4.5 points (Varni et al 2007), see the table below.

Table 19. Overview on QoL in pediatric patients (2 years and older) measured with PedsQL

	Baseline vs last changes PedsQL	Baseline vs best changes PedsQL
Greater or equal 4.5, n (%)	16 (66.67)	19 (79.17)
Less than 4.5, n (%)	8 (33.33)	5 (20.83)

Please note that the follow-up differs for all patients as the Vitrakvi® trial is still open for recruitment. The current median follow-up is 15.8 months (ePAS4). Hence the change in QoL might not be captured, while the best mean change might be more appropriate to focus on rather than the last measurement. In order to really capturer the QoL improvement the sustainability of the improvement shall be measured as well, please see the results in the table below. This quick improvement of QoL is in line with the median time to response being 1.8 months.

Table 20. Summary of QoL outcomes in adults and pediatric patients with TRK-fusion cancer

HRQoL Questionnaire	Adults EORTC QLQ-C30 Global Health Score	PedsQL (Children Aged ≥ 2 Years) Total Health Score
Patients with baseline and ≥ 1 postbaseline assessment, n	**74**	**24**
Patients with best postbaseline score above their baseline score, n (%)	51 (69)	21 (88)
Patients with best postbaseline score at or above MID[a] improvement, n (%)	44 (59)	19 (79)
Patients evaluable for sustained improvement (i.e., with baseline and ≥ 2 postbaseline assessments), n	**64**	**24**
Patients with sustained improvement lasting ≥ 2 consecutive cycles, n (%)	30 (47)	18 (75)
Patients with sustained improvement lasting until the end of assessments, n (%)	19 (30)	12 (50)

59% of the adult TRK fusion cancer patients meet the MID. Moreover, 79% of pediatric patients reach the MID improvement. The improvement is reported already within 2 months in the majority of patients. These results show that Vitrakvi® treatment in TRK fusion cancer patients lead to early and sustained improvement in QoL both in adult and pediatric patients. Hence, the threshold for the MID per the specified scale, with sustained improvement in QoL occurring in 40% of patients receiving Vitrakvi® is met according to the protocol specified.

Objective Response Rate

ORR is the primary outcome in the Vitrakvi® trial. The ORR is similar in the PAS-data and ePAS-data (July 2019). Overall the response rate is 79-80%.

Adults have an ORR of 71.4-74.4%. As shown in Table 21, almost all children respond to Vitrakvi® with an ORR of 94.5-100%. Also, the proportion CR is greater in children than in adults. Findings are similar in previous interim analysis (Drilon et al 2018 and Hong et al 2020).

For the Proxy-control arm BSC the ORR is 0%. For doxorubicin, the ORR is 14% of whom <1% is CR and 13% are PR. For the overall population Vitrakvi® has an ORR that is at least 65% greater than BSC/doxorubicin.

Table 21. Overall Response Rate per patient population

Population	**Overall population % (n)**		**Adult patients only % (n)**		**Pediatric patients only % (n)**	
Data-set / Outcome	PAS-data (n=55)	ePAS-data (n=164)	PAS-data (n=43)	ePAS-data (n=109)	PAS-data (n=12)	ePAS-data (n=55)
ORR, n (%)	44 (80.0)	130 (79.3)	32 (74.4)	78 (71.6)	12 (100)	52 (94.5)
CR, n (%)	13 (23.6)	(19.5)	8 (25.0)	11 (14.1)	5 (41.7)	21 (38.1)
PR, n (%)	31 (56.4)	(59.7)	24 (75.0)	67 (85.9)	7 (58.3)	31 (61.9)

Data cut-off: July 2019

As requested by the expert group in the protocol by MR, the ORR for each tumor type included is given below Table 22. Unfortunately, presentation of ORR per tumor type is misleading and produce divergent results. The main reason for this uncertainty is the rarity of TRK fusion cancers. As shown below in Table 22, the total number of patients in some tumor types is low, i.e. appendix cancer (n=2), hepatic cancer (n=1) etc. The most reliable ORR data can be found when the data is analyzed by including the whole population with TRK fusion cancer. These pooled data have been basis for EMA and FDA approval, resulting in the tumor agnostic indication as mentioned in the introduction. Results reported per tumor type and age are currently not available and hence not submitted.

Table 22. ORR per tumor type

	PAS-data (n=55)		**ePAS-data (n=164)**	
	Patients, n	**ORR, n (%)**	**Patients, n**	**ORR n (%)**
Appendix	1	0 (0)	1	0 (0)
Bone sarcoma	N/A	N/A	2	1 (50)
Breast	1	0 (0)	5	3 (60)
Cancer of unknown primary	N/A	N/A	1	1 (100)
Cholangiocarcinoma	2	0 (0)	2	0 (0)
Colon	4	1 (25)	8	3 (38)
Congenital mesoblastic nephroma	N/A	N/A	1	1 (100)
GIST	3	3 (100)	4	4 (100)
Hepatic	N/A	N/A	1	0 (0)
IFS	7	7 (100)	32	31 (97)
Lung	4	3 (75)	13	10 (77)
Melanoma	4	2 (50)	7	3 (43)
Pancreas	1	0 (0)	2	0 (0)
Prostate	N/A	N/A	1	0 (0)
Salivary gland	12	10 (83)	21	18 (86)
STS	11	10 (91)	36	29 (81)
Thyroid	5	5 (100)	27	15 (56)

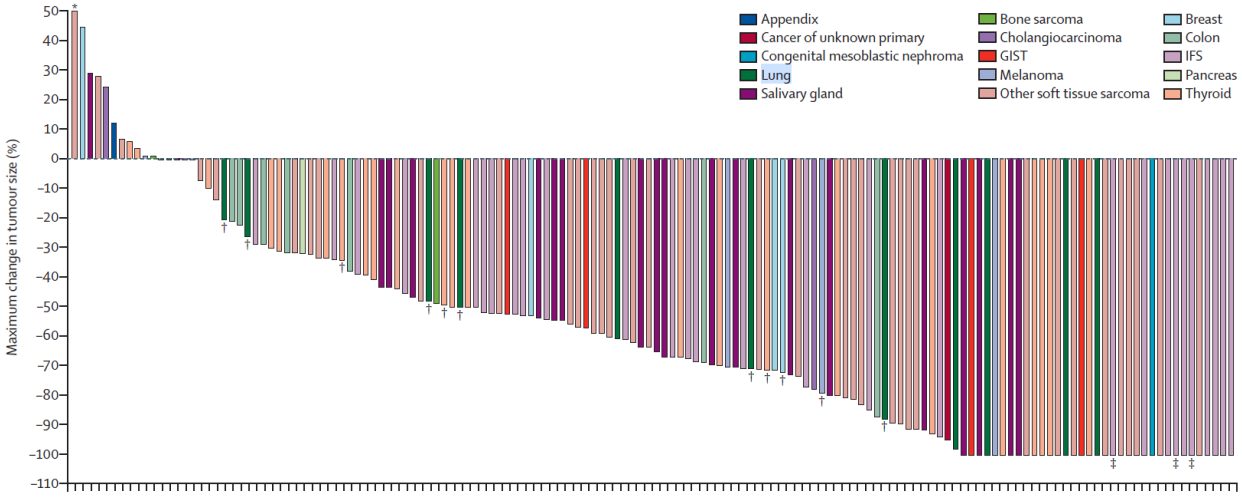
Data cut-off: July 2019

Similarly, further post-hoc analysis of the data will only lead to uncertainty. For example, the ePAS July 2019 data includes 17 different tumor types of which the majority include less than 10 patients per primary

location of the tumor. Hence, differences in OS-rate and PFS-rate at certain time-marks are not meaningful to be calculated in such rare diseases as TRK fusion cancer.

TRK fusion cancer is a genetically defined cancer and the tumor site of origin (i.e tumor type) is a minor variable in the pathologic description of the disease. NTRK gene fusion is the common denominator for the disease characteristics. The published data on the Vitrakvi® trial has shown that Vitrakvi® efficacy and safety is independent of the tumor location, please see figure 17 below (Drilon et 2018, Hong et 2020, Bayer data on file 2020). This demonstrates that the site of the tumor is not relevant for Vitrakvi® treatment and the mechanism of action of Vitrakvi® is independent of tumor location. Hence, Vitrakvi® treatment is entirely dependent on the presence/absence of NTRK fusion proteins i.e. if NTRK fusion-proteins are present Vitrakvi® is effective, and if they are not present Vitrakvi® is of no benefit.

Figure 17. Waterfall plot of the maximum percentage change in tumor size according to tumor type



Source: Hong et al 2020. Data cutoff February 2019.

Progression free survival: Median PFS

In the PAS-data (July 2019), the overall patient population has a median PFS of 25.8 (CI:9.9-NE) months at a median follow-up time of 31.4 months. In ePAS-data (July 2019) the median PFS is longer as the median PFS is 36.8 (CI: 25.7-NE) months with a median follow-up time of 13.8 months.

An earlier cut-off (February 2019) shows a median PFS of 25.8 months for PAS-data and 28.3 months for ePAS-data (n=159) (Hong et al 2020). Note that new patients are included and follow up time is longer for the ePAS-data in latest data cut-off. Data will soon be published in an updated SPC.

- As seen in Figure 18 and 19, the median PFS remains the same (PAS: median PFS 25.8 (CI:9.9-NE)) for PAS but changes for the extended data-set at later interim-analysis.

- For PAS-data, the median PFS remains unchanged at interim analysis February 2019 (Hong et al 2020) and latest data cut-off July 2019 (Data on file 2020) because no new patients are included and most importantly as numbers at risk do not change any further at 25.8 months where median PFS is measured. As Figure 18 and 19 show the numbers at risk increase only by one person (from 22 patients to 23 patients) at the time-point 24 months.

- Meanwhile in the extended data-set the numbers at risk increases with 5 new cases at a later interim-analysis (see Figure 20 and 21). The change in numbers at risk is based on increasing follow-up time and the inclusion of new patients. This is the same principal as for median OS. A detailed explanation is found in appendix 4. Median PFS is hence 36.8 months for ePAS-data (July 2019).

Figure 18. PFS for the overall patient population (n=55, PAS-data cut-off: Feb 2019)

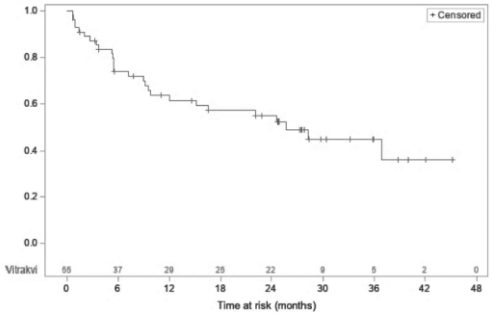


Figure 19. PFS for the overall patient population (n=55, PAS-data cut-off: July 2019)

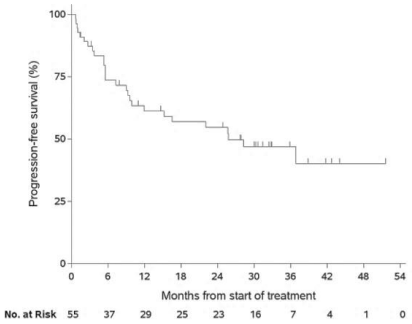


Figure 20. PFS for the overall patient population (n=153, ePAS-data cut-off: Feb 2019)

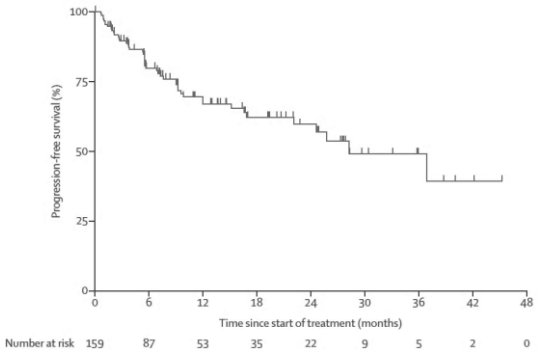
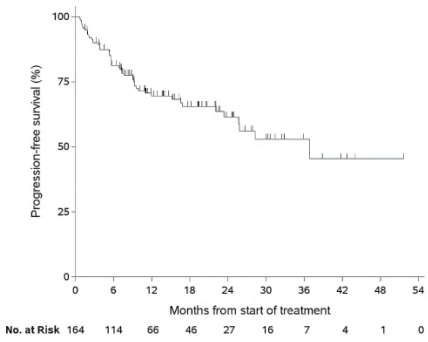


Figure 21. PFS for the overall patient population (n=164, ePAS-data cut-off: July 2019)



In the overall patient population, the median PFS for the Proxy-control arm BSC is 2.1 (0.7-3.7) months and 2.8 (1.9-5.3) months for PAS and ePAS-data respectively. For doxorubicin median PFS is 4.6 (2.9-5.6) months. Meanwhile the median PFS for the overall patient population in the Vitrakvi® arm is 25.8 (9.9-NE) months and 36.8 (25.7-NE) months for PAS and ePAS-data respectively. The minimum absolute difference of 3 months is hence met, see Table 23.

Bayer has also run an intra-patient comparison introduced by Von Hoff also called Growth Modulation Index (GMI). This measurement incorporates patients as their own control to minimize the risk of confounding factors. It is defined for individual patients as the ratio of progression-free survival (PFS) on current therapy to time to progression (TTP) with the preceding line of therapy (Von Hoff 1998). Hence, time to progression according to preceding treatment can be compared to time to progression on Vitrakvi® treatment. A detailed explanation is found in section 8.3. In short, patient have a median TTP on previous treatment line of 2.7 months. HR is 0.204 (95% CI: 0.144-0.288). The median TTP in the intra-patient comparison (2.7 months) is similar to median PFS for the Proxy-control arm BSC (2.1 months) and doxorubicin (2.8 months). Hence similar relative differences can be expected between Vitrakvi® and the proxy-control arm BSC and doxorubicin. Recently results per adult and pediatric have been published, please see section 8.3. for a detailed description. Note that the HR for adults is 0.27 (CI: 0.18-0.40) and for pediatrics 0.07 (CI: 0.03 - 0.16) (Italiano et al 2020).

As median PFS is a median value relative difference cannot be calculated. Nevertheless, we have conducted a t-test to analyse if the difference is statistically significant between the treatment alternative Vitrakvi® and doxorubicin. As seen in the table below Vitrakvi® has a statistically significant greater median PFS than doxorubicin. Median PFS is not reached when analysing pediatric patients separately as only 3 out of 12 patients in the PAS-data and 8 out of 55 patients in the ePAS-data have progressed.

Table 23. Median PFS for Vitrakvi® compared to doxorubicin

Median PFS	Vitrakvi®	Doxorubicin	Hypotestest
Overall population (ePAS4-data, July 2019)	36.8 (25.7 - NE)	4.6 (2.9 - 5.6)	t = 82.52 p <0.0001
Adult patients only (ePAS4-data, July 2019)	25.8 (15.2 - NE)	4.6 (2.9 - 5.6)	t = 55.29 p <0.0001

For adults only, the median PFS is similar to the overall patient population with a median PFS of 25.8 (15.2-NE) months (ePAS data July 2019).

Table 24. Median PFS for Vitrakvi® compared to the proxy-control arm BSC

Population	Intervention	N	Results	Absolut Difference
Overall population (PAS)	Vitrakvi®	55	25.8 (9.9-NE)*	23 months
	BSC	11	2.1 (0.7-3.7)	
Overall population (ePAS)	Vitrakvi®	164	36.8 (25.7-NE)**	34 months
	BSC	30	2.8 (1.9-5.3)	
Adult patients only (ePAS)	Vitrakvi®	109	25.8 (15.2-NE)	23 months
	BSC	30	2.8 (1.9-5.3)	
* at a median follow-up time of 31.4 months. ** at a median follow-up time of 13.8 months.				

Progression free survival: proportion of patients progression-free at 12-months

PFS is defined as time from randomization to progression or death. The expert group finds that an added clinical value is present in the case that there is a difference of 10% between Vitrakvi® and the comparator. For the Proxy-control arm BSC all patients either progressed or have been censored at the timepoint 12

months. In the doxorubicin arm we know that 26 out of 228 (11.4%) at 15 months are at risk for progression i.e. have not progressed.

In the Vitrakvi® arm 61-70% of the patients are progression free at 12-months for PAS and ePAS-data respectively, see the table below. For adults only (ePAS) the 62% are progression free at 12-months. In the pediatric population 86% of the patients are progression free at 12-months.

With the data above, the minimum clinical difference of 10% are met.

Table 25. Proportion of patients progression-free at 12-months

Population	Intervention	N	Results
Overall population (PAS)	Vitrakvi®	55	61% (48-75%)
	BSC	11	0%*
Overall population (ePAS)	Vitrakvi®	164	70% (62-77%)
	BSC	30	Not reached*
Adult patients only (ePAS)	Vitrakvi®	109	62 % (52-72%)
	BSC	30	Not reached*
Pediatric patients only (ePAS)	Vitrakvi®	55	86% (75-97%)
	BSC	30	Not reached*

Data cut-off: July 2019; * patient censored or have an event

Figures 22-25 show the PFS curves for the overall population and pediatric patients. Pediatric patients have a lower risk for progression over time compared to the overall patient population.

Figure 22. PFS for the overall patient population for Vitrakvi® (red) and BSC (blue) (PAS-data, n=55)

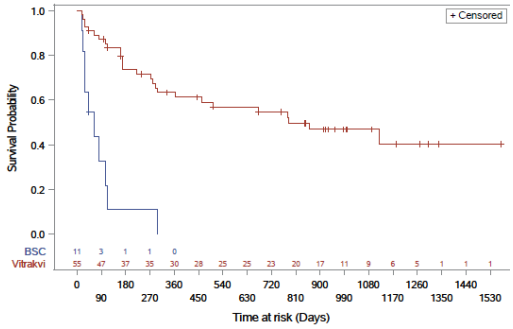


Figure 23. PFS for the overall patient population for Vitrakvi® (red) and BSC (blue) (ePAS-data, n=164)

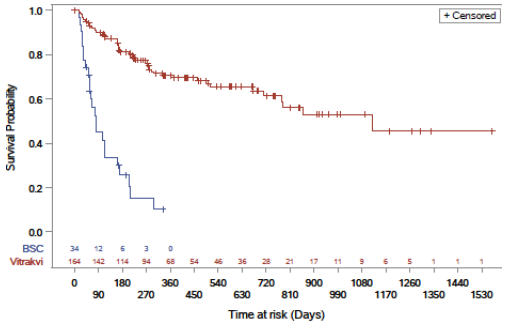


Figure 24. PFS for the pediatric population for Vitrakvi® (red) and BSC (blue) (PAS-data, n=12)

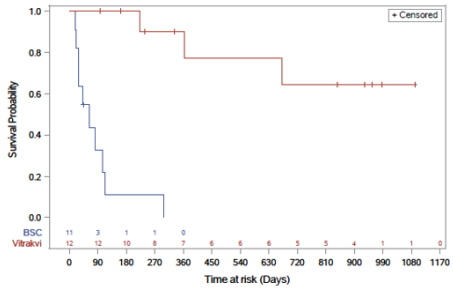
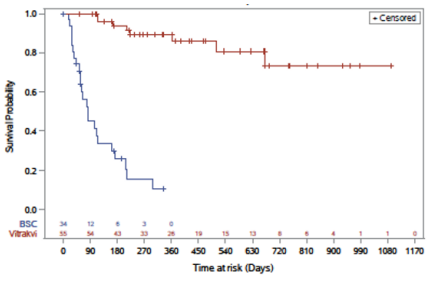


Figure 25. PFS for the pediatric population for Vitrakvi® (red) and BSC (blue) (ePAS-data, n=55)



Data cut-off: July 2019

Overview on adverse events

For the safety data there are several data-sets one being the integrated safety data which includes patients no with or without TRK fusion cancer from one of three studies: LOXO, SCOUT and NAVIGATE study and who received ≥1 dose of Vitrakvi®. Another safety data-set is per efficacy.

Here we will show the safety data for the overall patient population and then per adult and pediatric patients separately.

The latest available data is published by Hong et al (2020) showing the safety of Vitrakvi® evaluated in 260 patients with longer follow-up time than in the initial report (Drilon et al 2018), no new safety signals of Vitrakvi® have been identified, please see Table 26 (Hong et al 2020).

Adverse events (AEs) are primarily of grade 1 and 2 and the pattern and frequency similar across age groups. 39% and 7% of patients experienced grade 3 and 4 treatment-emergent AEs respectively. The most common grade 3 or higher treatment-emergent AEs are anemia and decreased neutrophil count. Grade 3 and 4 treatment related AEs are reported in 13% and 1% of patients respectively. The most common are increased alanine aminotransferase (3%), anemia (2%) and decreased neutrophil count (2%).

13 (5%) of 260 patients have serious AEs related to Vitrakvi®. Treatment-emergent AEs associated with death occurred in 5% (14/260) of patients overall and in 4% (6/159) of patients in the efficacy population with TRK fusion positive cancer. These are predominantly secondary to disease progression and none are deemed to be related to Vitrakvi®. No treatment-related deaths occurred.

Dose reduction due to AEs occurred in 8% of patients overall (22/260) and in 8% (13/159) of patients with TRK fusion positive cancer. The majority of adverse reactions leading to dose reduction occur in the first three months of treatment. Dose discontinuation due to treatment-related AEs occur in 2% (6/260) of patients, the most common of which is increased alanine aminotransferase: two of the six patients have TRK fusion positive cancer.

Table 26. Adverse events in the overall safety population (Hong et al 2020)

	Adverse events, regardless of attribution			Treatment-related adverse events	
	Grade 1–2	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	79 (30%)	6 (2%)	0	1 (<1%)	0
Alanine aminotransferase increased	64 (25%)	7 (3%)	2 (<1%)	7 (3%)	1 (<1%)
Cough	71 (27%)	1 (<1%)	0	0	0
Constipation	69 (27%)	1 (<1%)	0	0	0
Anaemia	44 (17%)	25 (10%)	0	6 (2%)	0
Aspartate aminotransferase increased	62 (24%)	6 (2%)	1 (<1%)	2 (<1%)	0
Dizziness	64 (25%)	2 (<1%)	0	1 (<1%)	0
Nausea	62 (24%)	2 (<1%)	0	2 (<1%)	0
Vomiting	62 (24%)	2 (<1%)	0	0	0
Diarrhoea	59 (23%)	3 (1%)	0	0	0
Pyrexia	50 (19%)	2 (<1%)	1 (<1%)	0	0
Dyspnoea	35 (13%)	6 (2%)	0	0	0
Myalgia	38 (15%)	3 (1%)	0	2 (<1%)	0
Peripheral oedema	40 (15%)	1 (<1%)	0	0	0
Headache	38 (15%)	1 (<1%)	0	1 (<1%)	0
Neutrophil count decreased	18 (7%)	12 (5%)	2 (<1%)	4 (2%)	1 (<1%)
Lymphocyte count decreased	22 (8%)	7 (3%)	2 (<1%)	2 (<1%)	0
Hypokalaemia	12 (5%)	8 (3%)	1 (<1%)	0	0
Hypophosphataemia	5 (2%)	9 (3%)	0	0	0

Data are n (%). n=260. The adverse events listed here are those that occurred at any grade in at least 15% of patients, or at grade 3 or worse in at least 3% of patients, regardless of attribution. Treatment-emergent adverse events occurring regardless of attribution in 10% or more of patients at grade 1 or 2 in severity, and all grade 3–5 events are presented in the appendix (pp 9–11).

The safety data for **adult patients** with TRK fusion cancer is recently published (Drilon et al 2020). Please note that the results are for the ePAS4 data and include 7 additional patients that have a follow-up time shorter 6 months as they have been recruited between the previous and last data cut-off (Feb 2019 - July 2019). 51% of the patients have one or more adverse events with grade 3-4. 8 patients (7%) have discontinued treatment due to treatment related adverse events (TEAE). Dose reduction has occurred in 12 patients (10%). There are 8 cases of TEAE related deaths (7%) where the majority of cases are due to progression of the underlying oncological disease or its complications. No deaths related to Vitrakvi® are reported.

The adverse events listed below are those that occurre in at least 15% of the patients, which is in line with the first publication of the Vitrakvi results (Drilion et al 2018).

A PDF-file ("TEAE in adults data cut-off July 2019") is shared with all adverse events that occurred in the adult patient population. The data is for the 116 patients outlined below meaning both 109 adult patients from the ePAS4 study and 7 additional patients (follow-up time shorter than 6 months).

Table 27. TEAE occurring in ≥15% of adult patients with TRK fusion cancer

Adult patients with TRK fusion cancer (n=116)	TEAEs, n (%)				Larotrectinib-related TEAEs, n (%)		
	Grade 1 or 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Dizziness	44 (38)	2 (2)	0	46 (40)	1 (1)	0	34 (29)
Fatigue	41 (35)	2 (2)	0	43 (37)	0	0	23 (20)
Constipation	40 (34)	0	0	40 (34)	0	0	18 (16)
ALT increased	30 (26)	3 (3)	2 (2)	35 (30)	3 (3)	2 (2)	29 (25)
Cough	33 (28)	1 (1)	0	34 (29)	0	0	1 (1)
Anemia	21 (18)	12 (10)	0	33 (28)	2 (2)	0	7 (6)
Nausea	31 (27)	1 (1)	0	32 (28)	1 (1)	0	15 (13)
Diarrhea	27 (23)	3 (3)	0	30 (26)	0	0	9 (8)
AST increased	26 (22)	2 (2)	1 (1)	29 (25)	2 (2)	1 (1)	26 (22)
Myalgia	28 (24)	1 (1)	0	29 (25)	1 (1)	0	17 (15)
Peripheral edema	29 (25)	0	0	29 (25)	0	0	11 (9)
Dyspnea	20 (17)	4 (3)	0	24 (21)	0	0	4 (3)
Arthralgia	23 (20)	0	0	23 (20)	0	0	6 (5)
Headache	22 (19)	0	0	22 (19)	0	0	8 (7)
Back pain	19 (16)	2 (2)	0	21 (18)	0	0	1 (1)
Weight increased	17 (15)	3 (3)	0	20 (17)	0	0	14 (12)
Pain in extremity	18 (16)	1 (1)	0	19 (16)	0	0	5 (4)
Vomiting	17 15)	0	0	17 (15)	0	0	7 (6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRK, tropomyosin receptor kinase.

The lastly published safety data for **pediatric patients** with TRK fusion cancer have been published at the conference for society of pediatric oncology in 2019 (Geoerger et al 2019) based on data cut-off from February 2019 including 52 pediatric patients. For information earlier results have been published by Laetsch et al 2018.

A PDF-file ("TEAE in pediatrics data cut-off July 2019") is shared with all adverse events that occurred in the current pediatric patient population with TRK fusion cancer. The data is for the 55 pediatric patients who are included in the ePAS4 study and 4 additional patients that have recently been recruited (follow-up time shorter than 6 months).

Table 28. Adverse events in pediatric patients (data cut off Feb 2019, n=52)

	Treatment-emergent adverse events (%)					Treatment-related adverse events (%)	
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3/4	Total
Vomiting	38	12	–	–	50	–	10
ALT increased	35	12	2	–	48	2	37
Pyrexia	31	12	2	2	46	–	–
AST increased	31	10	–	–	40	–	35
Cough	35	4	–	–	38	–	–
Diarrhoea	31	8	–	–	38	–	–
Neutrophil count decreased	4	12	15	4	35	10	23
Constipation	23	8	–	–	31	–	13
Fatigue	23	2	–	–	25	–	12
Leukocyte count decreased	19	4	–	–	23	–	13
Rhinitis	12	12	–	–	23	–	–
Upper respiratory tract infection	4	19	–	–	23	–	–
Anaemia	12	4	6	–	21	–	13
Blood alkaline phosphatase increased	15	6	–	–	21	–	13
Nasal congestion	17	4	–	–	21	–	–
Nausea	19	2	–	–	21	–	12

Proportion of patients with one or more adverse events with grade 3-4

The table below shows the proportion of patients with one or more adverse events with grade 3-4 for patients in the efficacy data set ePAS4 including 164 patients of whom 109 are adults and 55 pediatric (Data cut-off July 2019).

For the overall population the proportion of patients with one or more adverse events with grade 3-4 are 55% in the overall efficacy patient population. For adults 51% of the patients have one or more adverse events with grade 3-4 and for pediatric patients 64%.

We lack data for the comparator arm. Nevertheless, we can outline that doxorubicin has several adverse events of grad 3-4. Neutropenia occurred in 37% of the patients followed by leucopenia (18%), febrile neutropenia (13%), anaemia (4%) and thrombocytopenia (<1%) (Judson et al 2014).

The specific adverse events with grade 3-4) for the overall population are shared on a separately file called: "TEAE with severity grade 3 and 4_ePAS4"

Table 29. Proportion of patients with one or more adverse events with grade 3-4

Population	Intervention	N	Results
Overall population (ePAS)	Vitrakvi®	164	55%
	BSC	30	Not applicable
Adult patients only (ePAS)	Vitrakvi®	109	51%
	BSC	30	Not applicable
Pediatric patients only (ePAS)	Vitrakvi®	55	64%
	BSC	30	Not applicable

Data cut-off: July 2019

7.1.5 Discussion on comparative analysis

The Vitrakvi® trial is a single-arm multi-centre trial. The lack of a comparator arm is justified. If the study population would have been randomized into two treatment arms it would have taken many years before significant OS results could be shown and statistical power could be reached.

A comparator arm is established using a within trial comparison where patients with stable and progressive disease are validated to be a proxy for a control arm with BSC. This comparator is both validated and expanded with external data from a literature review identifying doxorubicin (Judson et al 2014) as well as the intra-patient comparison.

For outcomes outlined in the protocol, Bayer compared the available data between Vitrakvi® and the comparator. For all these outcomes (except adverse events due to lack of data), the presented minimal absolute difference outlined in the protocol by the expert group is above expectations. Relative difference or confidence intervals are calculated where possible. For OS-rate and PFS-rate, patients in the Proxy-control arm BSC have already had an event or been censored. There is no direct or indirect comparison available between Vitrakvi® and doxorubicin, which is why the data was presented narrative only. Relative differences are calculated afterwards where applicable.

Bayer finds that Vitrakvi® has a documented added clinical value compared to BSC. In addition, Bayer has also outlined the MCBS score where Vitrakvi® received the highest grade. Please see section 8.4. for more information.

8 Other considerations

8.1 Testing for TRK-fusion cancer

Sequencing (NGS), Whole Genome Sequencing (WGS), Immunohisto Chemistry (IHC), Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and Fluorescent In situ Hybridization (FISH).

Different tests have different benefits and limitations:

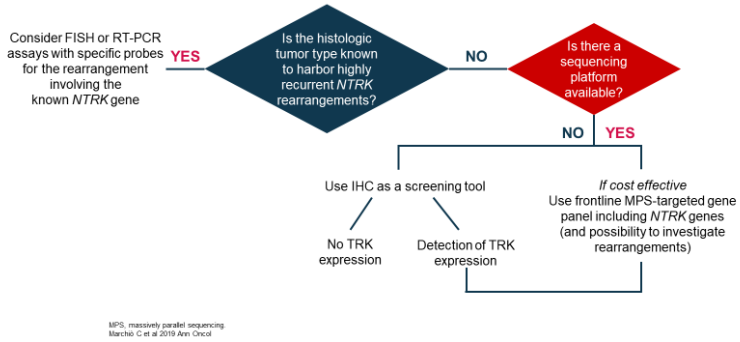
- **NGS testing:** Next Generation Sequencing provides a molecular profile of the patient's tumors and is a highly sensitivity test (Damodaran et al. 2017, Tan et al 2017).
    - DNA-based NGS testing: the test focuses on a selection of genes for a specific disease state. However, the ability to detect gene fusions is limited (Hechtman et al. 2017; Serrati et al. 2016).
    - RNA-based NGS testing: It can detect new fusion partners, which DNA-based cannot. Also, RNA-tests can test for the expression of a a specific gene product. RNA-based NGS testing requires a lower number of sequences reads compared to DNA-based NGS, which means the former has a faster sequencing process (Teixido et al 2018). There are also several gene-panels with hybrid of DNA- and RNA-based molecular profiles.
- **WGS testing**: sequencing of the whole genome
    - WGS testing provides the most comprehensive analysis of genetic variations. However, the test is costly compared to the other known methods and has one of the longest turnaround times for the available test methods (Serrati et al 2016).
- **IHC testing:** Immunohistochemistry
    - IHC testing is used by many centers due to the rapid ability to screen for the presence of fusion proteins. However, IHC testing can be challenging if there is no standardized scoring method for the protein expression. Hence, false positive and/or negative values can be obtained, and confirmation with NGS or other molecular methods are needed (Schram et al 2017).
- **FISH testing:** fluorescence in situ
    - FISH testing is largely considered the “gold standard” for detecting gene fusions in tissues. However, it can only detect a single fusion at a time (Hong et al. 2018). In this case TRK fusion cancer involves 3 genes and multiple fusion partners, designing multiple samples can be both time consuming and costly (Hong et al 2018).
- **RT-PCR testing:** reverse transcription polymerase chain reaction. RT-PCR testing is a commonly used test method where the advantage is that only a small tissue sample is required to detect genetic changes. However, other tests are preferred as it only detects a single known fusionpartner at a time and it is time consuming.

The identification of NTRK gene fusions in the Vitrakvi® trial is performed by the molecular test methods. NGS, RT-PCR and FISH. In the majority of cases (> 90%), NGS is used to detect NTRK gene fusions in approved laboratories (SmPC 2019). IHC is now used in several laboratories for screening patients to be confirmed with above molecular test methods. Hence, feasible guidelines are needed to identify patients for treatment.

ESMO recommendation uses a general proposal approach, in those malignancies where the *NTRK* fusions are described as pathognomonic or highly recurrent genetic alterations, such as the *ETV6–NTRK3* fusion gene in secretory carcinoma of the breast and of the salivary glands, congenital fibrosarcomas and cellular mesoblastic nephromas the detection of the fusion gene could be accomplished by FISH or RT-PCR. However, in those neoplasms where a limited proportion of cases is expected to harbor an *NTRK1/2/3* fusion and the

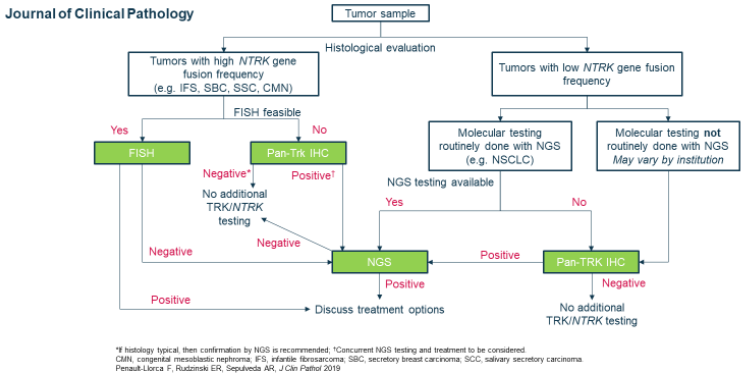
gene partner is unknown assays allowing for the detection of fusion genes in an agnostic manner would be indicated, either in the form of front-line NGS testing or by using a two-step approach involving a screening by immunohistochemistry (IHC) followed by NGS of cases expressing TRKA/B/C fusion proteins, please see figure 26 below for overview (Marchio et al 2019).

Figure 26. NTRK fusion detection: The ESMO proposal



There is also an algorithm by the Clinical Pathology Society which is based on the categorization of tumors into two groups based on the incidence of *NTRK* gene fusion. In tumors with a high frequency of *NTRK* gene fusion events, FISH is recommended, with pan-TRK IHC as an alternative if FISH is unavailable. Confirmation by targeted NGS in those cases with positive pan-TRK IHC can be conducted concurrently with treatment considerations. The pattern of TRK staining by IHC may also inform selection of a confirmatory test, as tumors harboring *NTRK1* rearrangements typically show strong, diffuse cytoplasmic staining. In contrast, tumors harboring *NTRK3* rearrangements may have weaker expression but often have at least focal nuclear staining. Negative results from FISH or pan-TRK IHC should be confirmed by NGS, although selection of a broader panel including other receptor tyrosine kinases is warranted as these tumors have a high likelihood of harboring other diagnostic and/or therapeutic alterations, please see Figure 27 below for overview (Penault Llorca et al 2019).

Figure 27. Testing algorithm for TRK fusion cancer based on tumor type



In solid tumors where gene fusions are common, but the frequency of *NTRK* gene fusions is lower (5%–25%), an NGS panel that includes *NTRK* fusions is recommended as the preferred test for patients. For tumors with a very low frequency of *NTRK* gene fusions (<5%), but where molecular screening is common, inclusion of *NTRK* genes in routine NGS analysis is recommended. For tumors with a low frequency of *NTRK* fusions, where NGS is not available or is not routinely performed for a tumor type, pan-TRK IHC should be performed for screening with NGS confirmation of positive IHC results (Penault Llorca et al 2019). Nevertheless, all proposals have to take in to account the strengths of the diagnostic technique and availability of each diagnostic technique at the centre.

Recently an international expert group discussed testing recommendations for specific patient groups with TRK fusion cancer. These recommendations have been agreed upon by representatives from the major oncology associations and has been summarised by Yoshino et al. The panel finds that the following patients should be tested:

- "Patients with advanced (unresectable or metastatic) solid tumours without actionable and driver gene mutations/fusions/amplifications should be tested for NTRK fusion."

- "Patients with advanced (unresectable or metastatic) solid tumours which are highly likely to harbour NTRK fusions should be tested for NTRK fusion, especially ETV6-NTRK3 fusion."

- "Patients with advanced (unresectable or metastatic) solid tumours other than above should be considered for testing for NTRK fusions."

- "Patients with locally-advanced tumours with a high incidence of NTRK fusion should be tested when considering neoadjuvant therapy before resection."

Also the time for testing is outlined and Yoshino et al suggest: "NTRK fusion testing should be considered prior to or during the standard treatment for advanced solid tumours."

When it comes to the method of testing; In situ hybridisation (FISH) and RT-PCR may be methods to use in tumors with a high likelihood of ETV6-NTRK3 fusions, FISH is not recommended for any other usage in NTRK fusion testing. IHC detects the TRK protein and not the TRK fusion. Positive IHC tests must always be confirmed by a NGS test. Depending on the individual lab capacity/equipment it could be a way to enrich possible NTRK fusion patients.

For sarcomas IHC seem to have a lower sensitivity and specificity and it might be reasonable to use NGS to analyse sarcomas for potential oncogenic drivers/biomarkers up front (Solomon et al).

8.2 Patient with TRK-fusion cancer with primary CNS tumors

Patients with primary CNS tumors are not included in efficacy data-sets PAS-data and ePAS-data.

There are several reasons that patients with primary CNS-tumor are to be evaluated separately: The Response Assessment in Neuro-Oncology (RANO) working group was established to improve the assessment of tumor response and selection of end points, specifically in the context of clinical trials. Among the challenges to use of earlier response criteria include lack of guidance on pseudo progression, pseudo response and non-enhancing tumor progression. Unlike RECIST, which measures uni-dimensional changes, RANO takes into account bi-dimensional measurements, as well as the use of corticosteroids. Further, the criteria for CR, PR, SD, and PD differ between RECIST 1.1 and RANO. For example, a 30% reduction counts as a PR in RECIST 1.1, while RANO requires 50% or more to be classified as a PR, and disease control rate (SD+PR+CR) is considered a more relevant effect measure in primary CNS tumors than overall response rate (ORR: PR+CR)

For these reasons the data is not combined with the PAS or ePAS data respectively but instead presented as an in-depended dataset. Note that patients with metastatic spread to the CNS are included in the PAS and ePAS data set.

Data has shown that Vitrakvi® is active in the CNS. In the latest interim analysis 24 patients with primary CNS tumors and measurable disease at baseline have been treated with Vitrakvi®. Their mean age is 8 years (range 1.3-79), 83% are pediatric and 54% female.

All primary CNS tumor patients have received prior cancer treatment (surgery, radiotherapy and/or previous systemic therapy). Tumor responses are assessed by the investigator using RANO or RECIST v1.1 criteria (SMPC 2019, Data on file Bayer).

Median PFS is 11 months at a median follow-up time of 5.6 months (range 3.6-13.8) at data cut-off July 2019. 63% have achieved disease control (SD). The ORR is 21% with 2 patients (8%) with a confirmed CR, 3 patients (13%) with a confirmed PR, 2 patients (8%) with a PR pending confirmation, 15 patients (63%) with an SD, and 2 patients (8%) with progressive disease.

The median time to response is 1.8 months. With a median duration of follow-up of 5.3 months (IQR: 3.6, 10.1), the median DOR is not reached at the time of this analysis (95% CI: 3.8, NE).

At 12 months 88% alive (Data on file Bayer). Median OS is not reached. The efficacy overview is also shown below by the waterfall plot. Note that the waterfall plot only shows 19 out of 24 patients since a waterfall plot only can show the change in tumor size for target lesions which is a measurable disease at baseline and post baseline. The other five patients are not accessed by either RANO or RECIST but by other parameters such as new lesions, change in non-target lesions etc.

Figure 28. PFS for patients with primary CNS and TRK fusion cancer

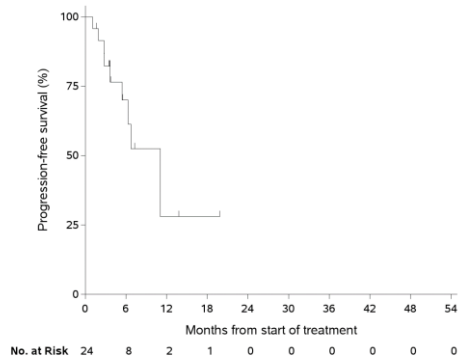


Figure 29. OS for patients with primary CNS and TRK fusion cancer

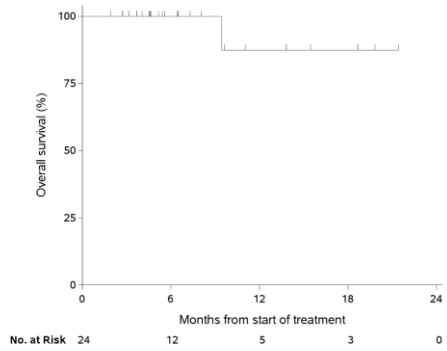
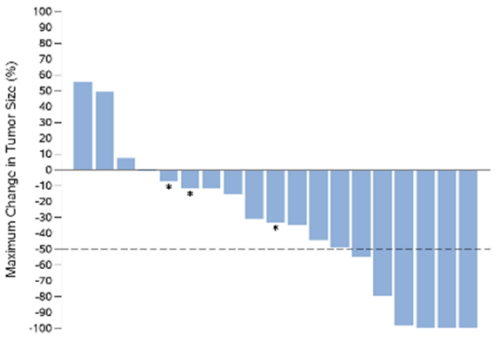


Figure 30: Waterfall plot of maximum change in tumor size among primary CNS tumor patients (Data cut-off: July 2019)



* RECIST v1.1 criteria are applied instead of RANO

The dotted line shows the 50% change in tumor size that is valid for patients evaluated according to the RANO criteria. Note that 3 patients are evaluated according to RECIST where a 30% thereshold is applied.

Although the majority of tumor types that harbour NTRK gene fusions do not typically metastasize to the CNS, some do, including lung cancer, thyroid cancer, and melanoma. For patients with such tumors, data suggest that Vitrakvi® achieved similar overall treatment outcomes in patients with pre-existing CNS metastases as in those without. These data, combined with the reported intracranial responses, suggest that Vitrakvi® is active within the CNS. The accrual of patients with primary CNS tumors is ongoing and outcome data will be published separately (Hong et al 2020).

8.3 GMI

Bayer has conducted an intra-patient comparison utilizing the innovative approach introduced by Von Hoff - the Growth Modulation Index (GMI). A self-comparison means the patient is controlled in terms of demographic factors and to a large extent clinical factors, with disease stage expected to decline over time making the analysis conservative with a bias against the later line treatment. Self-comparisons are highly relevant from a clinical perspective.

The GMI uses intra-patient comparison of successive time to progression (TTP) as a way to detect whether a new agent is having a modulating effect on tumor growth. Using a patient as his/her own control, the approach suggests that TTP tends to become shorter with successive lines of therapy. Given the natural history, one would expect time to progression to be shorter on the next treatment (TTPn) compared to the TTP on previous treatment (TTPn-1).

If a new agent has an anti-tumor effect, it will change the natural history of the disease so, if TTPn is greater than TTPn-1, then it is likely that the new agent is having an effect on the natural history of that patient's tumor.

GMI is the ratio of the TTPn and TTPn-1. For Vitrakvi® the GMI is calculated according to the following:

GMI = PFS (Vitrakvi®)/TTP-1 (Time on Progression with previous treatment before Vitrakvi®)

For this analysis, TTP_{-1} is calculated as the duration from prior therapy start date to date of progression or start of Vitrakvi® if date of progression is missing. This is a conservative approach assigning the longest duration to TTP_{-1} if date of progression is missing.

A sign of clinical activity is defined when the GMI value is ≥1.33 (Von Hoff 1998). The author outlines that "the threshold of 1.33 is arbitrary but considered excellent and unexpected for second-line therapy" and by extension to any new line of therapy.

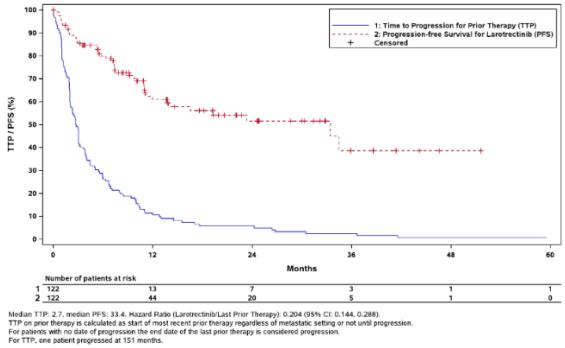
This analysis is performed on the 164 patients (ePAS, data cut-off July 2019). The analysis includes patients who have at least one prior therapy in any setting (122 patients). The median GMI assessed is 3.35 (range: 0.00 - 337.0) in the population with at least 1 prior therapy in any setting (n=122). The HR is 0.204 (95% CI: 0.144-0.288). As shown in Table 30, the majority of patients meet the threshold GMI of 1.33 in 68.9% in the population with at least 1 prior therapy in any setting (n=122).

Tabell 30: Growth Modulation Index (GMI)

	GMI
N	122
Mean (SD)	10.83 (37.53)
Median	3.35
Min, Max	0.00 - 337.0
GMI value	
<1	32 (26.2%)
≥ 1	90 (73.8%)
1 to 1.33	6 (4.9%)
≥ 1.33	84 (68.9%)

In GMI <1 category 6 patients are censored for PFS, GMI=growth modulator index

Figure 31. Intra-patient comparison: PFS-graph for Vitrakvi® (red) and time to progression for the same patients on their previous treatment (blue) (n=122, ePAS).



Data cut-off: July 2019

The majority of patients had a GMI ≥1.33 regardless of age as the figure below shows.

Figure 32. Waterfall plot of individual GMI values in the overall dataset (N=122) by age group (Italiano et al 2020)

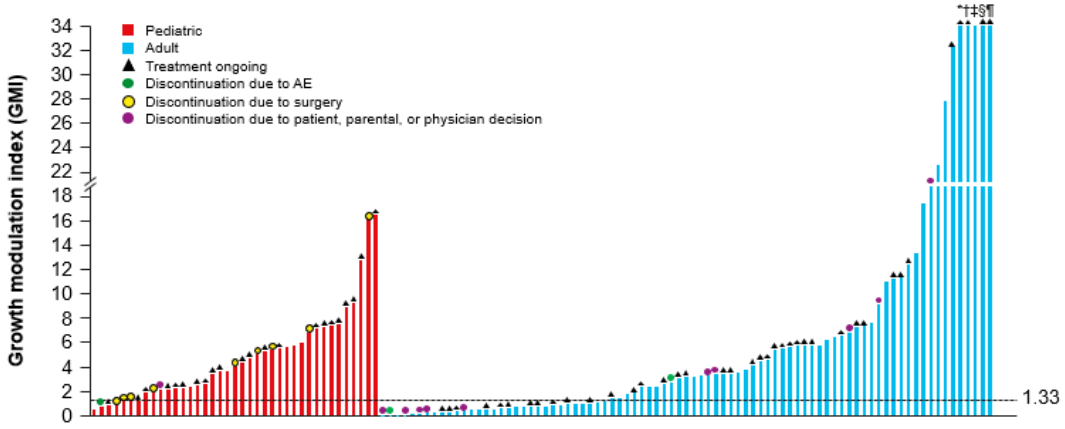
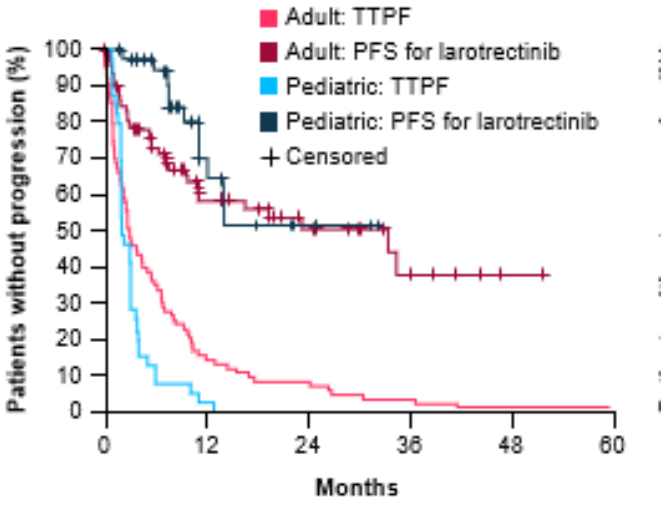


Figure 33 shows the intra-patient comparison for adults (n=83) and pediatrics (n=39) separately. The HR for adults is HR 0.27 (0.18-0.40) and for pediatrics HR 0.07 (0.03-0.16), showing that there is a significant reduced risk for progression for both adults and pediatric patients (Italiano et al 2020).

Figure 33. Intra-patient comparison: PFS-graph for Vitrakvi® (adults=dark red; pediatrics = dark blue) and time to progression for the same patients on their previous treatment (adults= red; pediatrics = light blue) (ePAS, July 2019) (Ref: Italiano et al 2020)



	Adult		Pediatric	
Median, months (95% CI)	3.0 (2.3, 5.1)	33.4 (10.9, NE)	2.0 (2.0, 3.0)	NR
HR (95% CI)	0.27 (0.18, 0.40)		0.07 (0.03, 0.16)	

8.4 ESMO evaluation according to Magnitude of Clinical Benefit Scare (MCBS)

ESMO developed a Magnitude of Clinical Benefit Scale (MCBS) that is dedicated to single-arm trials (Cherny 2017). MCBS includes several categories (Cherny 2017). Vitrakvi® falls under category 3, in line with the outline made by Medical Council Protocol.

Category 3 is the most relevant for single-armed studies in orphan diseases and with a high unmet need where the primary outcome is PFS or ORR. Hence, this category represents the Vitrakvi® trial.

This is the same scorecard outlined in the protocol and used previously for Vitrakvi® which can be found online at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-magnitude-of-clinical-benefit-scale/scorecard-143-1

The highest score is 3 for single-arm trials in orphan disease states or those with a high unmet need if the criteria's below are fulfilled: an ORR of >60%, or a median PFS >6 months, or an ORR ≥20% to <60% and a DOR ≥9 months (Cherny 2017).

Vitrakvi® has shown results in line with criteria above. For informative reasons we have prepared an overview for each outcome according to latest interim analysis in the table 31 below. Consequently, Vitrakvi® has been given the highest score, score 3, based on ESMO MCBS evaluation score (ESMO 2019).

Table 31. Overview on outcomes relevant for MCBS scale

	PAS (Drilon et al 2018) Data cut-off: July 2018	PAS (SPC August 2020) Data cut-off: July 2019	ePAS (SPC August 2020) Data cut-off: July 2019
ORR of >60%	Yes (80%)	Yes (79%)	Yes (80%)
median PFS >6 months	Yes (Not reached at a median follow-up time of 9,9 months)	Yes (25.8 months)	Yes (36.8 months)
Median DOR ≥9 months	Yes (Not reached at a median follow-up time of 8.3 months)	Yes (35.2 months)	Yes (Not reached at a median follow-up time of 13.8 months)

All outcomes investigator assessed.
Please note that these results shall remain confidential.

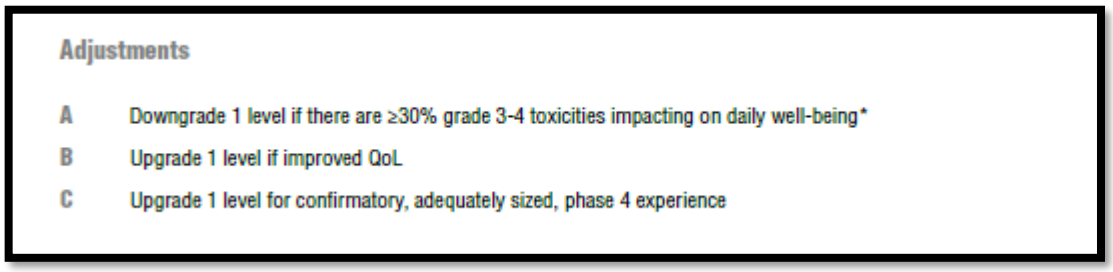
Vitrakvi® will also with follow-up data remain on the highest possible MCBS score meaning score 3.

In addition to what is requested in the scorecard above, there is also a request for the following information:

Table 32. Questions from the ESMO guidelines

Quality of life/Grade 3-4 toxicities* assessment	**Mark with √ if relevant**
Was QoL evaluated as secondary outcome?	QoL is evaluated as explanatory outcomes measured with EORTC QLQ-C30 in adults and PedsQL in pediatric patients above 2 years old.
Does secondary endpoint QoL show improvement?	Patients treated with Vitrakvi show an overall improvement in QoL. 69% (51 out of 74) and 88% (21 out of 24) of the adults and pediatric patients respectively have an improvement compared to their baseline assessment. The pre-specified meaningful threshold in improved QoL is shown for 59% of the adult patients and for 79% of the pediatric patients.
Are there ≥30% grade 3-4 toxicities impacting on daily well-being?*	No. Vitrakvi has few adverse events. Adverse events (AEs) are primarily of grade 1 and 2. The most common grade 3 or higher treatment-emergent AEs are anaemia and decreased neutrophil count. Grade 3 and 4 treatment related AEs are reported in 13% and 1% of patients respectively.
*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.	

Since all question above are answered, the scorecard is now asking for the following adjustments if necessary:



- Concerning point A (adverse events), no downgrading is necessary since Vitrakvi® does not have adverse events of grade 3-4 that occur equal or more than in 30% of the study population. Therefore, Vitrakvi® remains on score 3.
- Concerning point B (QoL), treatment with Vitrakvi® leads to improvement of QoL. As Vitrakvi® has already received the highest score, the score remains unchanged.
- Concerning point C (phase 4 study), the current clinical trial NAVIGATE is still recruiting and a phase 4 trial (ON-TREK) has started to include patients in the US, Germany and Austria. ON-TREK is planned to start also in Denmark but a pre-requisite for a phase 4 trial is that the product is prescribed in clinical practice – a positive recommendation from Medicinrådet is needed before the trial can start in Denmark. As Vitrakvi® already received the highest score, the score remains unchanged.

The score remains unchanged on level 3, which is the highest possible score in the ESMO-MAGNITUDE OF CLINICAL BENEFIT SCALE V1.1 (EVALUATION FORM 3).

Patients with primary CNS

Note, that patients with primary CNS and TRK fusion cancer also fulfil the highest score of the MCBS scale. One of the three outcomes need to be valid for reaching the highest score:

- an ORR of >60%, or
- median PFS >6 months, or
- ORR ≥20% to <60% and a DOR ≥9 months (Cherny 2017).

Patients with primary CNS have a median PFS of 11 months. Thereby the highest score is fulfilled. Note that point three also might be fulfilled but can first be answered after further follow-up time. At data cut-off July 2019 the ORR is greater than 20% and median DOR is not reached. Please see section 8.2. for further details.

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10 Appendices

10.1 Appendix 1. Literature search

	Inclusion criteria	Exclusion criteria
Population	TRK fusion cancer	
Intervention	Vitrakvi® (larotrectinib)	
Comparator(s)	Best Supportive Care (BSC)	No restrictions
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Overall Response Rate (ORR) • Quality of Life (QoL) • Adverse events	
Study design	Randomized control trials (phase I-III)*, observational studies	Non-interventional studies Case reports
Language restriction	English	
Publication dates	No restrictions	

*In the case that phase ll-III studies were available the respective phase I study was not included.

Search strategies

Table A1. shows the search strategy used in PubMed and Cochrane. Key search terms were as defined in the protocol (including different spelling and substance name):

Table A1.- Search strategy PubMed and Cochrane

Search Strategy	Hits
((((((((((((((larotrectinib[nm]) OR (larotrectinib[tiab] OR Vitrakvi®*[tiab] OR ARRY-470[tiab] OR LOXO-101[tiab])) OR ((NTRK[tiab] OR NTRK1[tiab] OR NTRK2[tiab] OR NTRK3[tiab]) AND (fusion[tiab] OR fusions[tiab]))) OR (neurotrophi*[tiab] AND (TRK[tiab] OR TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab]) AND (fusion[tiab] OR fusions[tiab]))) OR (neurotrophi*[tiab] AND tropomyosin receptor kinase*[tiab] AND (fusion[tiab] OR fusions[tiab]))) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND positive[tiab])) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND proteins[tiab])) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND (cancer[tiab] OR cancers[tiab])))) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]))) AND (((Observational Study[pt] OR Epidemiologic Studies[mh:noexp] OR Case Control Studies[mh] OR Cohort Studies[mh] or Cross-Sectional Studies[mh])) OR (observational[tiab] OR case control[tiab] OR cohort[tiab] OR cohorts[tiab] OR follow-up[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR cross sectional[tiab]))) NOT ((((((((((((((larotrectinib[nm]) OR (larotrectinib[tiab] OR Vitrakvi®*[tiab] OR ARRY-470[tiab] OR LOXO-101[tiab])) OR ((NTRK[tiab] OR NTRK1[tiab] OR NTRK2[tiab] OR NTRK3[tiab]) AND (fusion[tiab] OR fusions[tiab]))) OR (neurotrophi*[tiab] AND (TRK[tiab] OR TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab]) AND (fusion[tiab] OR fusions[tiab]))) OR (neurotrophi*[tiab] AND tropomyosin receptor kinase*[tiab] AND (fusion[tiab] OR fusions[tiab]))) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND positive[tiab])) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND proteins[tiab])) OR (TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND (cancer[tiab] OR cancers[tiab])))) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]))) AND ((Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh]))))	90
[larotrectinib:kw OR ((larotrectinib OR "ARRY 470" OR "LOXO 101"):ti,ab) OR (((NTRK OR NTRK1 OR NTRK2 OR NTRK3) NEAR/5 (fusion OR fusions)):ti,ab) OR (neurotrophi*:ti,ab AND (TRK OR TRKA OR TRKB OR TRKC):ti,ab AND (fusion OR fusions):ti,ab) OR (neurotrophi*:ti,ab AND (tropomyosin NEXT receptor NEXT kinase*):ti,ab AND (fusion OR fusions):ti,ab) OR (TRK:ti,ab AND (fusion OR fusions):ti,ab AND positive:ti,ab) OR (TRK:ti,ab AND (fusion OR fusions):ti,ab AND proteins:ti,ab) OR (TRK:ti,ab AND (fusion OR fusions):ti,ab AND (cancer OR cancers):ti,ab)" excluded conference abstracts	1

Figure A1. PRISMA Flow-chart

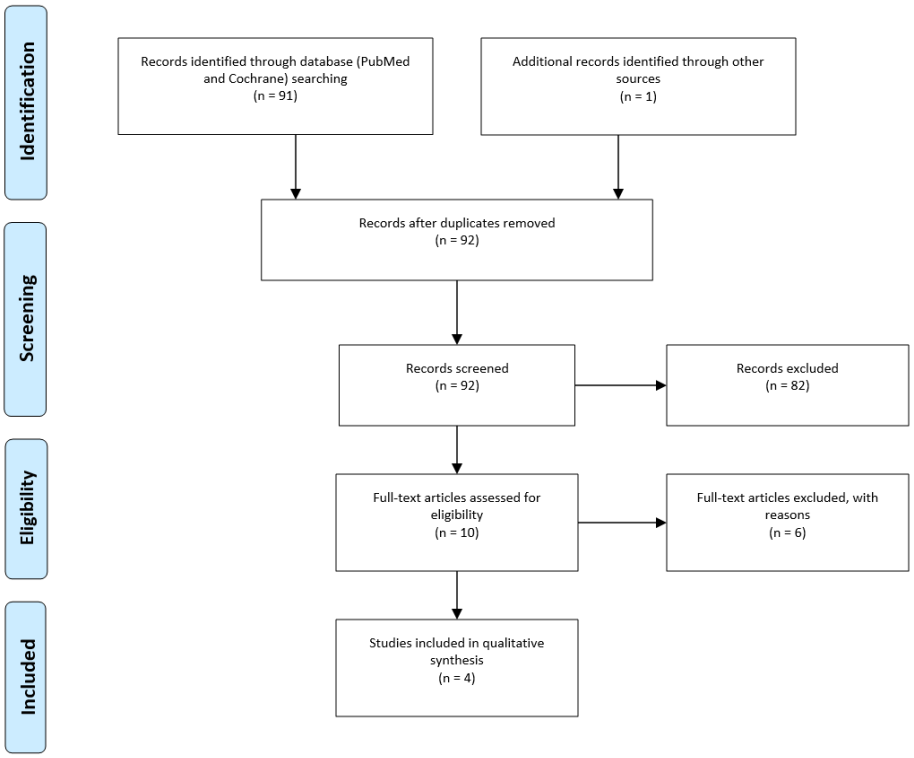


Table A2. Reason for exclusion of retrieved full-text articles

Reference	Reason for exclusion
Rosen, E.Y. et al (2020) TRK Fusions Are Enriched in Cancers with Uncommon Histologies and the Absence of Canonical Driver Mutations. Clinical Cancer Research.	Not reporting on neither the population nor clinical important outcomes that are defined in the protocol
Hong, D.S. et al (2019) Larotrectinib in adult patients with solid tumors: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol. 30(2):325-331.	Phase-I trial which results are covered in phase-II
Boon, E. et al (2018) Clinicopathological characteristics and outcome of 31 patients with ETV6-NTRK3 fusion gene confirmed (mammary analogue) secretory carcinoma of salivary glands. Oral Oncol. 82:29-33	No RCT and retropersective focus on surgery hence not reporting on clinical important outcomes that are defined in the protocol
Pietrantonio, F. (2017) ALK, ROS1, and NTRK Rearrangements in Metastatic Colorectal Cancer. J Natl Cancer Inst. 109(12).	Not reporting on neither the population nor clinical important outcomes that are defined in the protocol
Sartore-Bianchi, A. (2017) Pooled Analysis of Clinical Outcome of Patients with Chemorefractory Metastatic Colorectal Cancer Treated within Phase I/II Clinical Studies Based on Individual Biomarkers of Susceptibility: A Single-Institution Experience. Target Oncol. 12(4):525-533.	Not reporting on neither the population nor clinical important outcomes that are defined in the protocol
Lozano-Ortega, G. (2019) Tumor-specific randomized controlled trials in rare oncogene-driven cancers: asking for the impossible? Value in health. 22, S838-S839	Not reporting on clinical important outcomes that are defined in the protocol

10.2 Appendix 2. Main characteristics of included studies

<table>
<tr><td>Studie Name</td><td>Vitrakvi®-trial</td></tr>
<tr><td>NCT number</td><td>• Phase 1 adult clinical trial LOXO-TRK-14001 (NCT02122913)
• SCOUT, LOXO-TRK-15003 (NCT02637687)
• NAVIGATE, LOXO-TRK-15002 (NCT02576431)</td></tr>
<tr><td>Objective</td><td>To evaluate the efficacy and safety of Vitrakvi®</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>As previously explained, there are three clinical trials ongoing, which are pooled into a single analysis. The results for the primary analysis data-set which includes 55 patients was published in 2018 (Drilon 2018). Interim-analysis are continuously published. Current publications are:

• Drilon, A. et al (2018) Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 378(8): 731-739.
• DuBois, S.G. et al (2017) The use of larotrectinib in the management of locally advanced pediatric NTRK fusion sarcoma. Oral presentation at: Connective Tissue Oncology Society Annual Meeting; November 8-11, 2017; Maui, HI.
• Laetsch, T.W. et al (2018) Larotrectinib for pediatric solid tumors harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol. 19(5):705-714.
• Hong, D.S. et al (2020) Larotrectinib in patients with TRK fusion-positive solid tumors: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 1470-2045(19)30856-3.

Most recent data are currently on file but are expected to be presented at ASCO (June 2020) and included in the updated SPC for Vitrakvi® (August 2020).</td></tr>
<tr><td>Study type and design</td><td>The efficacy and safety of Vitrakvi® is studied in three multicentre trials, which are open-label and single-arm clinical studies in pediatric and adult patients. The phase 1 adult clinical study and the phase 1 enrolment of the pediatric study (SCOUT) included any patient with advanced solid tumors. This differs from the study design of the adult phase 2 NAVIGATE study, which was a trial design, including only patients with tumors harbouring a documented NTRK gene fusion. It should be noted that the phase 2 enrolment of the pediatric study (SCOUT) also included only patients with tumors harbouring a documented NTRK gene fusion. However, these patients are assigned to a cohort based on tumor location (intracranial vs extracranial). All studies are still ongoing. The studies were amended also to include primary CNS tumors.</td></tr>
<tr><td>Follow-up time</td><td>Trials are ongoing. Five- and three-years follow-up respectively for SCOUT and phase 1 adult/NAVIGATE studies are planned after closure of the studies.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Key inclusion criteria: Patients with a locally advanced or metastatic evaluable solid Tumor with a confirmed NTRK gene fusion who had previously received standard therapy, had an ECOG PS of 0 to 2, and had adequate major organ function were eligible for enrolment.
Key exclusion criteria: Patients who received previous treatment with kinase inhibitors with anti-TRK activity were excluded. Note: This was an early amendment to the phase 2 study and 1 patient was enrolled prior to the amendment who received such therapy.</td></tr>
<tr><td>Intervention</td><td>Dose differs for pediatric and adult patients. Pediatric receive a dose up to 100 mg/m2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution), the maximum dose is 100 mg per dose. Meanwhile adult patients are given 100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution). Treatment was given until disease progression or until unacceptable toxicity occurs.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Dataset</th><th>PAS</th><th>ePAS*</th><th>PAS
Adults only</th><th>ePAS
Adults only</th><th>PAS
Pediatrics only</th><th>ePAS
Pediatrics only</th></tr>
<tr><td>Data cut</td><td>Juli 2019</td><td>Juli 2019</td><td>Juli 2019</td><td>Juli 2019</td><td>Juli 2019</td><td>Juli 2019</td></tr>
<tr><td>Total patient population</td><td>55</td><td>164</td><td>43</td><td>109</td><td>12</td><td>55</td></tr>
<tr><td>Median follow-up time, months</td><td>31,8</td><td>14,5</td><td>31,2</td><td>14,3</td><td>32,8</td><td>15.3</td></tr>
<tr><td>Median age, years</td><td>45 (range 0.3-76)</td><td>42 (0,05-84)</td><td>57 (24-76)</td><td>56 (19-84)</td><td>1,8 (0,33-12)</td><td>1,2 (0,05-14)</td></tr>
<tr><td>Amount of children, %</td><td>21,8</td><td>34,2</td><td>0</td><td>0</td><td>100</td><td>100</td></tr>
<tr><td>Amount of women, %</td><td>47</td><td>52</td><td>47</td><td>0,53</td><td>50</td><td>47</td></tr>
<tr><td>Performance status, %</td><td>ECOG</td><td>ECOG</td><td>ECOG</td><td>92</td><td>ECOG</td><td>ECOG</td></tr>
<tr><td>0 or 1</td><td>93,0</td><td>86,0</td><td>93,0</td><td>84,4</td><td>92,0</td><td>91,0</td></tr>
<tr><td>>=2</td><td>7,0</td><td>14,0</td><td>7,0</td><td>15,6</td><td>8,0</td><td>9,0</td></tr>
<tr><td>≥1 earlier treatment (%)</td><td>80</td><td>78</td><td>79,1</td><td>80,7</td><td>83,0</td><td>74,0</td></tr>
</table>
</td></tr>
</table>

	Primary tumor location	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS)	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS), Hepatic, Bone sarcoma, Congenital mesoblastic nephroma, prostate	Appendix, Breast, Cholangiocarcinoma, Colon, GIST, Lung, Melanoma, Pancreas, Salivary gland, Soft tissue sarcoma and Thyroid	Appendix, Bone sarcoma, Breast, Cancer of unknown primary, Cholangiocarcinoma, Colon, GIST, Hepatic, Lung, Melanoma, Prostate, Salivary gland, Soft tissue sarcoma, Tyroid	Infantile fibrosarcoma, soft tissue sarcoma	Melanoma, Soft tissue sarcoma, IFS, Congenital mesoblastic nephroma, Thyroid
Primary and secondary endpoints	The primary endpoint for efficacy analyses was ORR. Duration of response, safety, OS and PFS were included as secondary endpoints. QoL was included as an exploratory endpoint. Tumor responses were assessed by using RANO or RECIST v1.1 criteria.						
Method of analysis	Kaplan–Meier method is used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.						
Subgroup analyses	Patients with primary CNS tumor						

Results from previous data cut-off July 2017 by Drilon et al (2018)

Study	Efficacy of Vitrakvi in TRK Fusion–Positive Cancers in Adults and Children, Drilon A et al, 2018, N Engl J Med 2018;378:731-9. DOI: 10.1056/NEJMoa1714448
Study design	Three multicentre basket trials; open label and single arm clinical studies in adult and pediatric NTRK gene fusion positive cancer patients
Patient population	Eligible patients had a locally advanced or metastatic solid tumor, had received standard therapy previously (if available), had an Eastern Cooperative Oncology Group performance-status score of 0 to 3 (on a scale from 0 to 5, with higher scores indicating greater disability), and had adequate major organ function. An early amendment to the phase 2 study involving adolescents and adults prohibited previous treatment with kinase inhibitors with anti-TRK activity, although one such patient was enrolled before this amendment.
Intervention	Patients who enrolled in the phase 1 studies involving adults and children were treated during the dose-escalation portion of those studies. The phase 2 study involving adolescents and adults used the recommended dose of 100 mg of Vitrakvi twice daily, administered orally continuously. For children who had a body-surface area of less than 1 m2, a twice-daily dose of 100 mg per square meter was selected. A liquid formulation was available for patients who were unable to swallow capsules. The drug was administered continuously until disease progression, withdrawal of the patient from the study, or the occurrence of an unacceptable level of adverse events.
Comparator	N/A
Follow-up time	See «Øvrige rapporterte utfallsmål med resultater»
Primary outcomes	By INV assessment and data-cutoff date July 2017 (n=55) ORR (95% CI): 80% (67% - 90%) Complete response: 16%* Partial response: 64% Stable disease: 9% Progressive disease: 11% Could not be evaluated: 0% (*including 1 patient with a pathological complete response)
Secondary outcomes	As of data-cutoff date July 2017: The *median duration of response* had not been reached after a median follow-up duration of 8.3 months (range, 0.03+ to 24.9+ [plus signs indicate ongoing response at the time of data cutoff]). The *median progression-free survival* had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9+)

Results from previous data cut-off February 2019 by Hong et al (2020)

Study	Vitrakvi in patients with TRK fusion-positive solid tumors: a pooled analysis of three phase 1/2 clinical trials. Hong et al (2020) Lancet Oncol 2020 https://doi.org/10.1016/S1470-2045(19)30856-3
Study design	Three multicentre basket trials; open label and single arm clinical studies in adult and pediatric NTRK gene fusion positive cancer patients
Patient population	The protocols for the three individual clinical studies detailing full eligibility criteria and the statistical analysis plan for the integrated analysis have been previously reported (Drilon et al 2018). Briefly, eligible patients were aged 1 month or older, had a locally advanced or metastatic solid tumor, had received standard therapy previously (if available), and had adequate organ function. Eligibility criteria in relation to life expectancy, performance status, comorbidities and previous treatments not permitted or permitted (and washout periods), and laboratory test values required to assess eligibility varied across the contributing studies and are detailed in the individual trial protocols. Patients with both treated and untreated brain metastases were eligible, provided these metastases were not symptomatic. Patients with primary CNS tumors were eligible for the trials, but were excluded from the current analysis, which was focused on patients with Response Evaluation Criteria in Solid Tumors (RECIST)-measurable disease. TRK fusion positivity was determined by locally obtained molecular testing using either next generation sequencing, FISH, or reverse transcriptase PCR. An implied TRK fusion based on *ETV6* break-apart FISH positivity was considered acceptable for patients with infantile fibrosarcoma because *NTRK3* was the only gene fusion partner reported with *ETV6* in infantile fibrosarcoma and given the high frequency of *ETV6*– *NTRK3* fusions in this disease
Intervention	Vitrakvi was administered orally (capsule or liquid formulation), continuously, on a 28-day schedule. In the phase 2 study, all adult and adolescent patients received the recommended starting dose of 100 mg twice daily. In the phase 1 studies, several patients were included from the dose escalation stage. The majority of pediatric patients (43 [83%] of 52) received 100 mg/m² per dose (maximum of 100 mg) twice daily, with a minority (nine [16%] of 52 patients) receiving other doses. Vitrakvi was administered until disease progression, withdrawal of the patient from the study, or the occurrence of an unacceptable level of adverse events.
Comparator	N/A
Follow-up time	See «Øvrige rapporterte utfallsmål med resultater»
Primary outcomes	By INV assessment and data-cutoff date February 2019 (n=153) ORR (95% CI): 79% (72% - 85%) Complete response: 16%* Partial response: 63% Stable disease: 12% Progressive disease: 6% Not determined: 3% (*including 3 patients with pathological complete response)
Secondary outcomes	As of data-cutoff date February 2019: The *median duration of response* was 35·2 months (95% CI 22·8–not estimable [NE]) The *median progression-free survival* was 28·3 months (95% CI 22·1–[NE]) Seven patients stopped treatment after surgery with curative intent.

10.3 Appendix 3. Overview on clinical effectiveness of doxorubicin in patients with STS (Judson et al 2014)

Bayer has run the second search strategy outlined in appendix 2 in the MR protocol for Vitrakvi:

Table 1. Search strategy for effectiveness of the comparator arm

((((((((((((((((((((((((((((((solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti])))) OR ((soft tissue[ti] OR soft-part[ti] OR connective tissue[ti]) AND (sarcoma[ti] OR sarcomas[ti] OR cancer[ti] OR cancers[ti])))) OR (angiosarcoma[ti] OR hemangiosarcoma[ti] OR chondrosarcoma[ti] OR fibromyxosarcoma[ti] OR fibrosarcoma[ti] OR infantile fibrosarcoma[ti] OR myxofibrosarcoma[ti] OR leiomyosarcoma[ti] OR liposarcoma[ti] OR malignant mesenchymoma[ti] OR malignant mesenchymal tumor[ti] OR neurofibrosarcoma[ti] OR rhabdomyosarcoma[ti] OR synovial sarcoma[ti] OR spindle cell sarcoma[ti])) OR (bone cancer[ti] OR bone sarcoma[ti] OR Ewing sarcoma[ti] OR osteosarcoma[ti])) OR (MASC[ti] OR mammary analogue secretory carcinoma[ti])) OR ((salivary[ti] OR parotid[ti] OR submandibular[ti] OR sublingual[ti]) AND (gland[ti] OR glands[ti]) AND (masc[ti] OR cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR ((bowel[ti] OR colon[ti] OR colonic[ti] OR colorectal[ti] OR rectal[ti] OR rectum[ti] OR sigmoid[ti] OR intestinal[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR ((thyroid[ti] OR parathyroid[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR (gastrointestinal stromal[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti]))) OR GIST[ti]) OR (lung[ti] AND (adenocarcinoma[ti] OR carcinoma[ti]))) OR (NSCLC[ti] OR non-small cell lung cancer[ti] OR nonsmall cell lung cancer[ti])) OR melanoma[ti]) OR cholangiocarcinoma[ti]) OR ((bile duct*[ti] OR biliary duct*[ti]) AND (carcinoma[ti] OR cancer[ti]))) OR ((appendiceal[ti] OR appendix[ti]) AND (cancer[ti] OR carcinoma[ti]))) OR (breast[ti] AND secretory[ti] AND (carcinoma[ti] OR carcinomas[ti]))) OR congenital mesoblastic nephroma[ti]) OR ((pancreatic[ti] OR pancreas[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR (primary[ti] AND (CNS[ti] OR central nervous system[ti] OR brain[ti]) AND (cancer[ti] OR tumour[ti] OR tumor[ti] OR lymphoma[ti]))) OR (glioblastoma[ti] OR glioma[ti] OR astrocytoma[ti] OR oligodendroglioma[ti] OR primary cerebral lymphoma[ti]))) AND (metastatic[ti] OR metastasis[ti] OR metastases[ti] OR advanced[ti] OR recurrent[ti] OR refractory[ti])) AND ((((((((((treatment resistant[tiab] OR treatment resistance[tiab] OR chemotherapy resistant[tiab])) OR (incurable[tiab] OR "no cure"[tiab] OR untreatable[tiab])) OR late stage[tiab]) OR (Terminally Ill[mh] OR Terminal Care[mh] OR (terminal[tiab] NOT terminal half-life[tiab]) OR terminally[tiab])) OR (best supportive care[tiab] OR active supportive care[tiab] OR optimal supportive care[tiab] OR supportive care alone[tiab] OR supportive care only[tiab])) OR (symptomatic treatment[tiab] OR symptomatic therapy[tiab] OR experimental treatment[tiab] OR late-line[tiab])) OR (Palliative Care[mh] OR palliation[tiab] OR palliative[tiab] OR palliatively[tiab])) OR (eol care[tiab] OR end of life[tiab])))) AND ((Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh]))) AND English[la])) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Meta-Analysis[pt] OR News[pt] OR Observational Study[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR meta-analysis[tiab] OR review[ti] OR Retrospective Studies[mh] OR retrospective[ti] OR systematic review[tiab])

The most likely therapy to be given to TRK fusion cancer patients in clinical practice is a chemotherapy. Patients in the Vitrakvi trial are in an advanced disease stage as they are metastatic, have local advanced cancer or are not eligible for surgery. The treatment of choice currently for those patients is chemotherapy since chemo therapy is the antitumor therapy used when the patients no longer have any other appropriate alternative.

Doxorubicin as a representation of chemotherapy was chosen

- as it is used in a wide range of histologies,
- as it is considered a relatively efficacious and safe therapy, and
- since sarcomas were the most frequent tumor histology in the Vitrakvi clinical trials (sarcomas comprised the majority of histologies in which NTRK gene fusion cancer manifested in the Vitrakvi trial (PAS, N=55) being STS: 20%, IFS: 13%, GIST: 5% and in total 38%)

A mono therapy, like doxorubicin, has the same effect as other chemo therapies. Also, combination therapies with chemo therapies do not have any effect advantage versus a mono therapy but instead cost more, the comparison versus doxorubicin must be viewed as a conservative approach. Thus, we included doxorubicin as an inclusion criterion in the literature review.

According to its SmPC, doxorubicin is indicated in small cell lung cancer, breast cancer, advanced ovarian carcinoma, bladder cancer, osteosarcoma, advanced soft tissue sarcoma, Ewings sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphatic leukemia, acute myeloblastic leukemia, multiple myeloma,

endometrial carcinoma, Wilms tumor, papillary and follicular thyroid cancer, anaplastic thyroid cancer and neuroblastoma (SmPC doxorubicin). Hence, a study investigating the efficacy and safety of doxorubicin in locally advanced or metastatic STS is a logical source of comparator data both to sarcoma treatments and a tumor agnostic treatment.

According to the search strategy in Table 1 above 418 articles are found. With the inclusion criteria that doxorubicin is mentioned in the title/abstract, two articles are found:

- Judson et al (2014) Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet; 15 (4): 415-423.
- Cullinan et al (1985) A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. Jama; 256 (14):2016-7.

Judson et al (2014) has the longest follow-up time, similar baseline characteristics to the Vitrakvi trial and is also the most recent publication, which is why Judson et al is included to represent the effectiveness of doxorubicin and used for the comparison to Vitrakvi® and validation of the proxy-control arm.

One must compare Vitrakvi to doxorubicin as last-line anti tumoral therapy, in cases when no other therapy is available or surgical resection is not possible. We note that Judson et al evaluates doxorubicin as a first line therapy. The effectiveness of chemotherapy in a later stage (second, third or later) does not produce better results on PFS and OS compared to first line treatment. Thus, doxorubicin as monotherapy is a relevant and conservative alternative for the validation of the proxy-control-arm. Using another chemotherapy in a later stage would give Vitrakvi a greater advantage as the difference in probability of PFS and OS would increase, and the costs as other alternatives are more expensive. Another validation with another chemotherapy is hence not necessary.

Table 2. Overview of Judson et al (2014)

<table>
<tr><td>Study</td><td>Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial, Judson, I. et al, 2014, Lancet Oncol 2014; 15: 415–23</td></tr>
<tr><td>Study design</td><td>Phase 3 randomized controlled trial</td></tr>
<tr><td>Patient population</td><td>Patients with locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma, age 18–60 years with a WHO performance status of 0 or 1</td></tr>
<tr><td>Intervention</td><td>Doxorubicin (75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion) as first-line treatment</td></tr>
<tr><td>Comparator</td><td>Intensified doxorubicin (75mg/m²; 25 mg/m² per day, days 1–3) plus ifosfamide (10 g/m² over 4 days with mesna and pegfilgrastim) as first-line treatment</td></tr>
<tr><td>Follow-up time</td><td>Median follow-up was 56 months (IQR 31–77) in the doxorubicin only group and 59 months (36–72) in the combination group</td></tr>
<tr><td>Primary outcomes</td><td>In the doxorubicin group
mOS (95.5% CI): 12.8 months (10.5–14.3)
mPFS (95.5% CI): 4.6 months (2.9–5.6)</td></tr>
<tr><td>Secondary outcomes</td><td>
<table>
<tr><th>Efficacy parameter</th><th>Doxorubicin group (n=228)</th><th>Doxorubicin and ifosfamide group (n=227)</th></tr>
<tr><td>Overall response rate</td><td>13%</td><td>27%</td></tr>
<tr><td>Complete response</td><td>1 (0%)</td><td>4 (2%)</td></tr>
<tr><td>Partial response</td><td>30 (13%)</td><td>56 (25%)</td></tr>
<tr><td>Stable disease</td><td>105 (46%)</td><td>114 (50%)</td></tr>
<tr><td>Progressive disease</td><td>74 (32%)</td><td>30 (13%)</td></tr>
<tr><td>Early death (progression)</td><td>4 (2%)</td><td>5 (2%)</td></tr>
<tr><td>Early death (other cause)</td><td>3 (1%)</td><td>2 (1%)</td></tr>
<tr><td>Not evaluable</td><td>11 (5%)</td><td>16 (7%)</td></tr>
<tr><td>“Cured”, %</td><td>0*</td><td>N/A</td></tr>
</table>
</td></tr>
</table>

	Follow-up (median, months)	56	59	

Table 3. Comparison of baseline characteristics from Judson and Vitrakvi clinical trial

Publication	**Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial (Judson et al 2014)**	**PAS July 2019**	**ePAS4 July 2019**
Population	Adult patients with high-grade soft-tissue sarcoma with unresectable or metastatic disease progression within 6 weeks before treatment	Patients with a locally advanced or metastatic solid tumor (excluding primary CNS) who had previously received standard therapy or had no other option than amputation or disfiguring surgery, had an ECOG PS of 0 to 2, and had adequate major organ function.	Patients with a locally advanced or metastatic solid tumor (excluding primary CNS) who had previously received standard therapy or had no other option than amputation or disfiguring surgery, had an ECOG PS of 0 to 2, and had adequate major organ function.
N	228	55	164
Follow-up, months, median	56.4	31.8	14.5
Age, years, median	48 (range 18-60)	45 (range 0.3-76)	42 (range 0.05-84)
Pediatric, %	0	21.8	34.2
Female, %	55	47	52
Performance status, %	WHO	ECOG	ECOG
0	45	44	49
1	43	49	38
>=2	<1	7	14
At least one previous systemic therapy (%)	0	80	78
BOR CR, %	<1	24	19
BOR PR, %	13	56	60
mOS, months	12.8 (CI 10.5–14.3)	NR	NR
mPFS, months	4.6 (CI 2.9–5.6)	25.8 (CI 9.9-N.E.)	36.8 (CI 25.7-N.E.)
Site of active disease	Different soft tissue sarcoma types: undifferentiated pleomorphic sarcoma, myxoid or round cell liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, synovial sarcoma, myxofibrosarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumour, epithelioid sarcoma, unclassified high-grade sarcoma (not otherwise specified))	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon, Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS)	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon, Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS), Hepatic, Bone sarcoma, Congenital mesoblastic nephroma, Prostate

10.4 Appendix 4. Why is median OS not shown in the latest interim analysis?

The explanation for the median OS being reported in the earlier cut-off but not in the latter lies in the methodology of Kaplan-Meier survival analysis:

The medians are not a crude median, but instead a median estimated by Kaplan-Meier (KM) Methodology, which is standard in oncology and not specific to Vitrakvi®.

The Kaplan-Meier methodology is more complicated than just looking at the median value of the full population. The population at risk changes over time for several reasons:

- individual patients are not followed long enough, and hence these patients can still move the median with more follow-up data
- drop outs for other reasons than death, who are then censored from the analysis

Below the KM graph (here example OS), the number of patients at risk over time can be seen. We have many censorings along the chart, which reduces the number of patients at risk significantly to e.g. only 8 at 36 months. This means that at 36 months, only 8 patients were still at risk of dying because all other patients have either not been followed up for 36 months or have died before.

The KM methodology, accounts for varying number of patients at risk to account for patients with limited follow up or drop outs for other reasons. This is why by KM methodology, the median can be reached, even if there were far less than 50% events (relating to the full population).

With more follow up time, the censored patients will move further to the right. The number of patients at risk in the later months increases then, making the steps smaller again. This is why the median has not been reached in the latest data cut-off.

Figure 1 and 3 below illustrates the OS-curves for the PAS-data and the ePAS-data at the cut-off point in February 2019 leading to the indication that duration of median OS is 44.4 months. The reason, however, is because at the 36-month time-mark of the study, only 8 patients are at risk for an event. The other patients has either not been followed-up for 36 months or died already. With the low number of patients at risk, each event has a greater bearing. One death causes a decrease of the Kaplan-Meier curve by 33.3%, as shown in Figure 1 and 3 below between 42 months and 48 months.

This changes at the next follow-up point. As stated above, patients are moving to the right on the X-axis in the Kaplan-Meier graph, which increases the number of patients at risk and hence minimizes the bearing of each event. Hence, median OS is not reached at the later data cut-off even tough median follow-up time is 32.5 months for PAS-data and 15.8 months for ePAS-data.

Figure 1. Kaplan-Meier graph for OS for patients in the extended data-set (n=159)

Data cut-off: Feb 2019

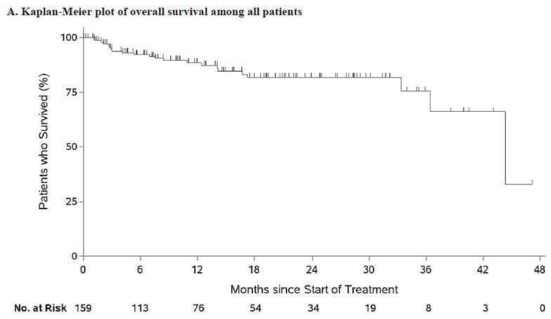


Figure 2. Kaplan-Meier graph for OS for patients in the extended data-set (n=164*) Data cut-off: July 2019

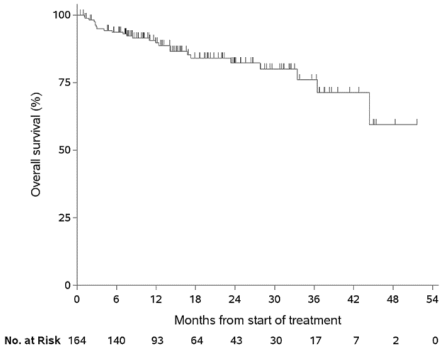


Figure 3. Kaplan-Meier graph for OS for patients in the primary data-set (n=55)

Data cut-off: Feb 2019

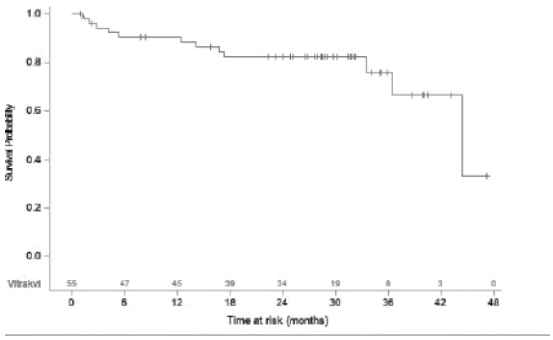
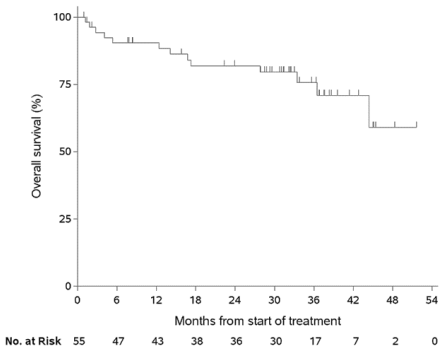


Figure 4. Kaplan-Meier graph for OS for patients in the primary data-set (n=55)

Data cut-off: July 2019



*Between February and July data cut-off, 5 more patients have been included as the trial is ongoing

10.5 Appendix 5.

Overview on results per study for the PAS data set (July 2019)

Trial name:	Vitrakvi trial		
NCT number:	NCT-02122913, NCT-02637687, NCT-02576431		
Outcome	Study arm	N in arm	Result (CI)
Median OS	Vitrakvi-arm	55	Not reached
OS-rate at 24-months	Vitrakvi-arm	55	82% (71-93%)
Median PFS	Vitrakvi-arm	55	25.8 (9.9-NE)
Proportion of progression free patients at 12-months	Vitrakvi-arm	55	61% (48-75%)
Patients with a pathological complete response	Vitrakvi-arm	55	5.5% (3 out of 55)
ORR	Vitrakvi-arm	55	80% (67% - 90%)
			CR 23.6%
			PR 56.4%

Overview on results per study for the ePAS4 data set (July 2019)

Trial name:	Vitrakvi trial		
NCT number:	NCT-02122913, NCT-02637687, NCT-02576431		
Outcome	Study arm	N	Result (CI)
Median OS	Vitrakvi-arm	164	Not reached
OS-rate at 24-months	Vitrakvi-arm	164	82% (75-90%)
Median PFS	Vitrakvi-arm	164	36.8 (25.7-NE)
Proportion of progression free patients at 12-months	Vitrakvi-arm	164	70% (62-77%)
Patients with a pathological complete response	Vitrakvi-arm	164	6.1% (10 out of 164)
ORR	Vitrakvi-arm	164	79% (72%- 85%)
			CR 19.5%
			PR 59.7%

Results per main PICO for the overall population

Please see section 7.3.1. to obtain a detailed overview on each PICO outcome as well as QoL and adverse events. There also effect in subgroups are presented: adult patients and pediatric patients. The results below are based on ePAS4 data from data cut-off July 2019.

Results per outcome for the overall patient population			Absolute difference in effect			Relative difference in effect		
	Treatment arm (Ref)	Results	Difference to Vitrakvi	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value
Median OS	Median OS is not reached in the Vitrakvi trial.							
OS-rate at 24-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	82% (75 – 90%) All patients died or are censored 28% (22 – 34%)	54%	NR	NR	0.199	(0.143 - 0.278)	p<0.0001
Median PFS	Vitrakvi arm Proxy-control arm Doxorubicin arm	36.8 (25.7 - NE) 2.8 (1.9-5.3) 4.6 (2.9 - 5.6)	34 months 23 months	NR	NR	Not applicable. We have run a t-test instread. Please see Table 17.		
Proportion of progression free patients at 12-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	70% (62-77%) 0% patients have been censored or had an event Circa 12 % No confidence interval reported	70% 58%	NR NR	NR NR	In an intra-patient comparison Vitrakvi has been compared to the effect seen on previous treatment within the same patient population. Thereby time to progression on previous treatment could be compared to progression free survival with Vitrakvi. The HR is 0.204 (95% CI: 0.144-0.288). The median time to progression in the intra-patient comparison (2.7 months) is similar to median PFS for the Proxy-control arm BSC (2.1 months) and doxorubicin (2.8 months). Hence similar relative differences can be expected between Vitrakvi® and the proxy-control arm BSC and doxorubicin.		
ORR	Vitrakvi arm Proxy-control arm Doxorubicin arm	79% (72%-85%) 0 14%	65%	NR	NR			
QoL	Data is available only by adults and pediatrics separately.							
Proportion of patients with one or more adverse events with grade 3-4	Vitrakvi arm Proxy-control arm	55% NA						

Results per main PICO for the adult population

Please see section 7.3.1. for all PICO factors and explanation.

Results per outcome for the overall patient population			Absolute difference in effect			Relative difference in effect		
	Treatment arm (Ref)	Results	Difference to Vitrakvi	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value
Median OS	Median OS is not reached in the Vitrakvi trial.							
OS-rate at 24-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	76% (66 – 86%) All patients died or are censored 28% (22 – 34%)	48%	NR	NR	0.261	(0.185 - 0.368)	p<0.0001
Median PFS	Vitrakvi arm Proxy-control arm Doxorubicin arm	25.8 (15.2 - NE) 2.8 (1.9-5.3) 4.6 (2.9-5.6)	23 months 21.2 months	NR	NR	Not applicable. We have run a t-test instread. Please see Table 17.		
Proportion of progression free patients at 12-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	62% (52-72%) 0% patients have been censored or had an event Circa 12 % No confidence interval reported	62% 50%	NR NR	NR NR	In an intra-patient comparison Vitrakvi has been compared to the effect seen on previous treatment within the same patient population. Thereby time to progression on previous treatment could be compared to progression free survival with Vitrakvi. The HR is 0.204 (95% CI: 0.144-0.288). The median time to progression in the intra-patient comparison (2.7 months) is similar to median PFS for the Proxy-control arm BSC (2.1 months) and doxorubicin (2.8 months). Hence similar relative differences can be expected between Vitrakvi® and the proxy-control arm BSC and doxorubicin.		
ORR	Vitrakvi arm Proxy-control arm Doxorubicin arm	71.6% 0 14%	57,6%	NR	NR			
QoL	Vitrakvi arm Proxy-control arm	70.61 NA	-	-	-	QoL is evaluated via a comparison between QoL at baseline vs last changes. QoL at baseline is 64.98 and at last visit 70.61. 36% experience a clinical improvement in QoL.		
Proportion of patients with one or more adverse events with grade 3-4	Vitrakvi arm Proxy-control arm	51% NA	-	-	-	-	-	-

Results per main PICO for the pediatric population

Please see section 7.3.1. for all PICO factors and explanation.

Results per outcome for the overall patient population			Absolute difference in effect			Relative difference in effect		
	Treatment arm (Ref)	Results	Difference to Vitrakvi	CI	*P* value	Hazard/Odds/Risk ratio	CI	*P* value
Median OS	Median OS is not reached in the Vitrakvi trial.							
OS-rate at 24-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	95% (89 – 100%) All patients died or are censored 28% (22 – 34%)	 67%	 NR	 NR	 0.061	 (0.040 - 0.095)	 p<0.0001
Median PFS	Vitrakvi arm Proxy-control arm Doxorubicin arm	Not reached meaning patient are progression free 2.8 (1.9-5.3) 4.6 (2.9-5.6)	 23 months 21.2 months	 NR	 NR	Not applicable. We have run a t-test instread. Please see Table 17.		
Proportion of progression free patients at 12-months	Vitrakvi arm Proxy-control arm Doxorubicin arm	86% (75-97%) 0% patients have been censored or had an event Circa 12 % No confidence interval reported	 86% 74%	 NR NR	 NR NR	In an intra-patient comparison Vitrakvi has been compared to the effect seen on previous treatment within the same patient population. Thereby time to progression on previous treatment could be compared to progression free survival with Vitrakvi. The HR is 0.204 (95% CI: 0.144-0.288). The median time to progression in the intra-patient comparison (2.7 months) is similar to median PFS for the Proxy-control arm BSC (2.1 months) and doxorubicin (2.8 months). Hence similar relative differences can be expected between Vitrakvi® and the proxy-control arm BSC and doxorubicin.		
ORR	Vitrakvi arm Proxy-control arm Doxorubicin arm	94.5% 0 14%	 80.5%	 NR	 NR	 	 	
QoL	Vitrakvi arm Proxy-control arm	82.98 N/A				QoL is evaluated via a comparison between QoL at baseline vs last changes. QoL at baseline is 68.13 and at last visit 82.98. 67% experience a clinical improvement in QoL.		
Proportion of patients with one or more	Vitrakvi arm	64%						

adverse events with grade 3-4	Proxy-control arm	N/A						

10.6 Appendix 6. Literature search 2.

Bayer has run the second search strategy outlines in appendix 2 in MR protocol for Vitrakvi:

Table 1. Search strategy for effectiveness of the comparator arm
((((((((((((((((((((((((((((((solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti])))) OR ((soft tissue[ti] OR soft-part[ti] OR connective tissue[ti]) AND (sarcoma[ti] OR sarcomas[ti] OR cancer[ti] OR cancers[ti])))) OR (angiosarcoma[ti] OR hemangiosarcoma[ti] OR chondrosarcoma[ti] OR fibromyxosarcoma[ti] OR fibrosarcoma[ti] OR infantile fibrosarcoma[ti] OR myxofibrosarcoma[ti] OR leiomyosarcoma[ti] OR liposarcoma[ti] OR malignant mesenchymoma[ti] OR malignant mesenchymal tumor[ti] OR neurofibrosarcoma[ti] OR rhabdomyosarcoma[ti] OR synovial sarcoma[ti] OR spindle cell sarcoma[ti])) OR (bone cancer[ti] OR bone sarcoma[ti] OR Ewing sarcoma[ti] OR osteosarcoma[ti])) OR (MASC[ti] OR mammary analogue secretory carcinoma[ti])) OR ((salivary[ti] OR parotid[ti] OR submandibular[ti] OR sublingual[ti]) AND (gland[ti] OR glands[ti]) AND (masc[ti] OR cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR ((bowel[ti] OR colon[ti] OR colonic[ti] OR colorectal[ti] OR rectal[ti] OR rectum[ti] OR sigmoid[ti] OR intestinal[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR ((thyroid[ti] OR parathyroid[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR (gastrointestinal stromal[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti]))) OR GIST[ti]) OR (lung[ti] AND (adenocarcinoma[ti] OR carcinoma[ti]))) OR (NSCLC[ti] OR non-small cell lung cancer[ti] OR nonsmall cell lung cancer[ti])) OR melanoma[ti]) OR cholangiocarcinoma[ti]) OR ((bile duct*[ti] OR biliary duct*[ti]) AND (carcinoma[ti] OR cancer[ti]))) OR ((appendiceal[ti] OR appendix[ti]) AND (cancer[ti] OR carcinoma[ti]))) OR (breast[ti] AND secretory[ti] AND (carcinoma[ti] OR carcinomas[ti]))) OR congenital mesoblastic nephroma[ti]) OR ((pancreatic[ti] OR pancreas[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti]))) OR (primary[ti] AND (CNS[ti] OR central nervous system[ti] OR brain[ti]) AND (cancer[ti] OR tumour[ti] OR tumor[ti] OR lymphoma[ti]))) OR (glioblastoma[ti] OR glioma[ti] OR astrocytoma[ti] OR oligodendroglioma[ti] OR primary cerebral lymphoma[ti]))) AND (metastatic[ti] OR metastasis[ti] OR metastases[ti] OR advanced[ti] OR recurrent[ti] OR refractory[ti])) AND (((((((((treatment resistant[tiab] OR treatment resistance[tiab] OR chemotherapy resistant[tiab])) OR (incurable[tiab] OR "no cure"[tiab] OR untreatable[tiab])) OR late stage[tiab]) OR (Terminally Ill[mh] OR Terminal Care[mh] OR (terminal[tiab] NOT terminal half-life[tiab]) OR terminally[tiab])) OR (best supportive care[tiab] OR active supportive care[tiab] OR optimal supportive care[tiab] OR supportive care alone[tiab] OR supportive care only[tiab])) OR (symptomatic treatment[tiab] OR symptomatic therapy[tiab] OR experimental treatment[tiab] OR late-line[tiab])) OR (Palliative Care[mh] OR palliation[tiab] OR palliative[tiab] OR palliatively[tiab])) OR (eol care[tiab] OR end of life[tiab])))) AND ((Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh]))) AND English[la])) NOT (Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Meta-Analysis[pt] OR News[pt] OR Observational Study[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR meta-analysis[tiab] OR review[ti] OR Retrospective Studies[mh] OR retrospective[ti] OR systematic review[tiab])

This search results in 418 articles. With the inclusion criteria that doxorubicin is mentioned in the title, two articles are found:

- Judson et al (2014) Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet; 15 (4): 415-423.
- Cullinan et al (1985) A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. Jama; 256 (14):2016-7.

Judson et al (2014) has the longest follow-up time, similar baseline characteristics to the Vitrakvi® trial and is also the most recent publication, which is why Judson et al is included to represent the effectiveness of doxorubicin.

10.7 Appendix 7. Patients with TRK fusion cancer with the primary tumor located in the lung or thyroid

With the continuous recruitment of patients, data per tumor type increases both in patients and median follow-up time. During ESMO treatment specific results have been published for patients with TRK fusion cancer where the tumor is located in the lung or thyroid.

In a pooled analysis of adult and pediatric patients (N=164) with TRK fusion cancer treated in three clinical trials, Vitrakvi® has an ORR of 79.3%, a median PFS of 36.8 months, and not reached median OS (ePAS4, July 2019).

In patients with TRK fusion cancer who's tumor is primary located in the lung, the ORR is similar to the overall population (ORR=71%) with an ORR of 57% for patients with CNS metastases (Drilon et al 2020: ESMO). Median PFS and median OS are not reached at data cut-off July 2019, see the figure below.

Figure A7.1. Baseline characteristics

	Patients with TRK fusion lung cancer (N=14)
Age, years, median (range)	52 (25–76)
Sex, n (%)	
Male	8 (57)
Female	6 (43)
Presence of CNS metastases, n (%)	7 (50)
Prior therapies*, n (%)	
Surgery	9 (64)
Radiotherapy	8 (57)
Systemic therapy†	13 (93)
Number of prior systemic therapies, median (range)	3 (1–5)
Number of prior systemic therapies, n (%)	
0	1 (7)
1	4 (29)
2	2 (14)
≥3	7 (50)
Best response to prior therapy, n (%)	
Partial response	2 (14)
Stable disease	4 (29)
Progressive disease	4 (29)
Other	4 (29)

Figure A7.2. Waterfall plot: Vitrakvi® in patients with TRK fusion cancer primary located in the lung

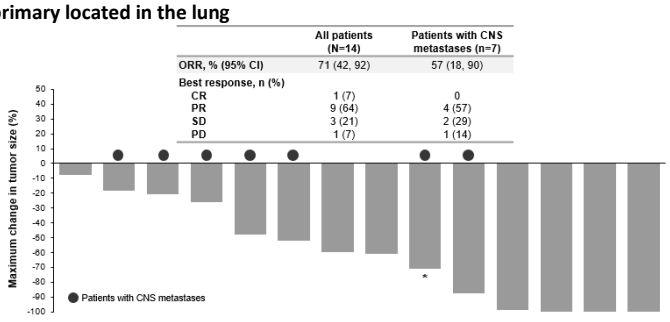
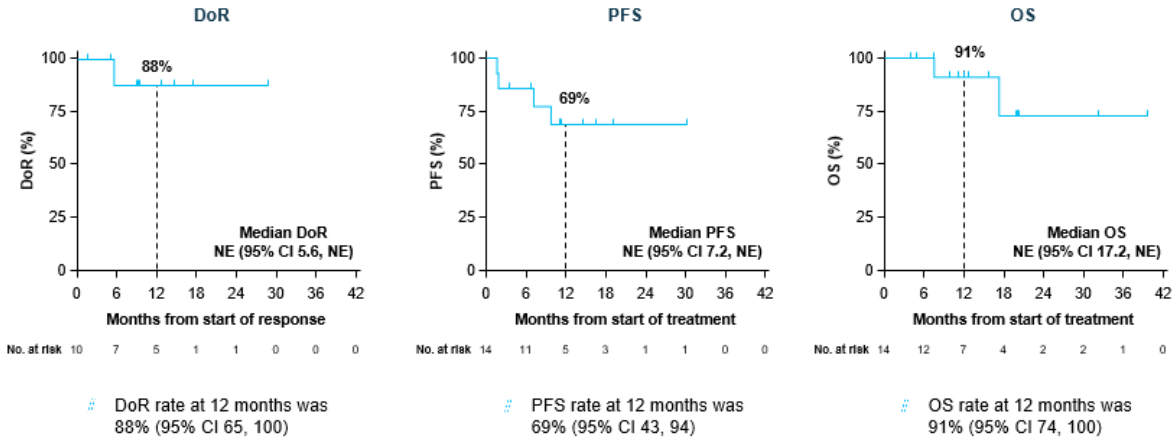


Figure A7.3. KM figure: DoR, PFS and OS for Vitrakvi® in patients with TRK fusion cancer primary located in the lung



Adverse events are similar to the overall population (Drilion et al 2020: ESMO)

In patients with TRK fusion cancer who's tumor is primary located in the thyroid, the ORR is similar to the overall population (ORR=75%) but lower for patients with anaplastic thyroid tumors (ORR=29%) (Cabanilas et al 2020). Median PFS is not reached and median OS is currently measured to 27.8 months at data cut-off July 2019, see the figures below.

Figure A7.4. Baseline characteristics

	Patients with TRK fusion thyroid cancer (N=28)
Age, years, median (range)	61.5 (6.0–80.0)
Pediatric (<18 years), n (%)	2 (7)
Adult (≥18 years), n (%)	26 (93)
Sex, n (%)	
Male	9 (32)
Female	19 (68)
Presence of CNS metastases, n (%)	4 (14)
***NTRK* gene fusion, n (%)**	
NTRK1	12 (43)
NTRK2	0
NTRK3	16 (57)
Prior therapies,* n (%)	
Surgery	28 (100)
Radiotherapy	17 (61)
RAI	22 (79)
Systemic therapy†	16 (57)
Number of prior systemic therapies, n (%)	
0	12 (43)‡
1	7 (25)
2	7 (25)
≥3	2 (7)

Figure A7.5. Waterfall plot: Vitrakvi® in patients with TRK fusion cancer primary located in the thyroid

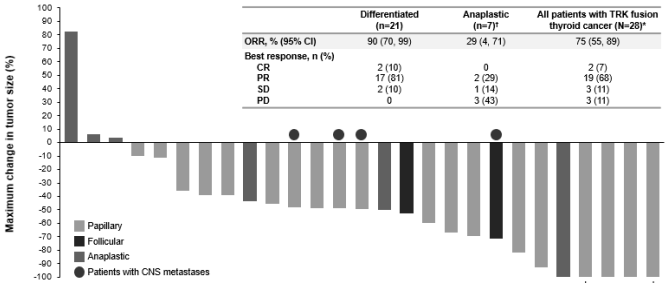
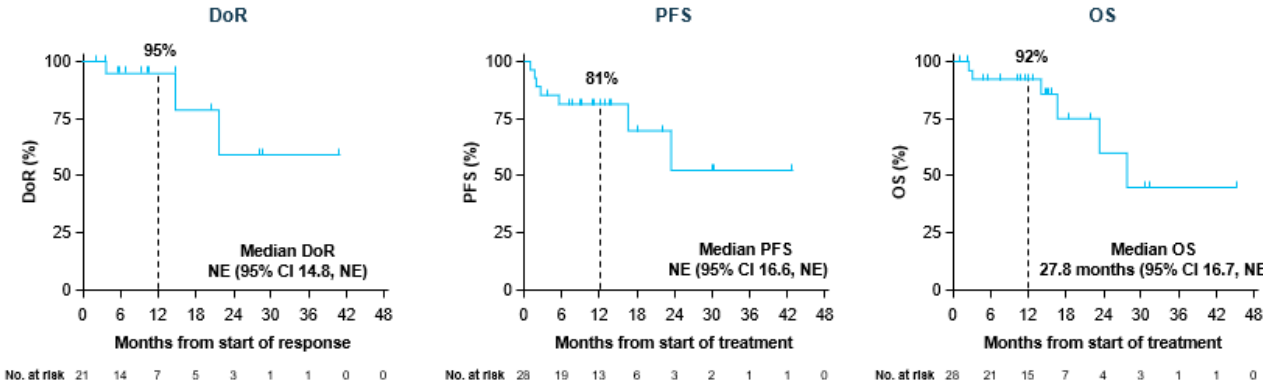


Figure A7.5. KM figure: DoR, PFS and OS for Vitrakvi® in patients with TRK fusion cancer primary located in the thyoid



‡ DoR rate at 12 months was 95% (95% CI 85, 100)

‡ PFS rate at 12 months was 81% (95% CI 67, 96) and at 18 months was 70% (95% CI 45, 94)

‡ OS rate at 12 months was 92% (95% CI 82, 100)

Final technical and economical section of the application for the assessment of Vitrakvi® (larotrectinib)

Vitrakvi® as monotherapy is indicated for the treatment of paediatric and adult patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion:

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity
- and who have no satisfactory treatment options

Contents

1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

Proprietary name	Vitrakvi®
Generic name	Larotrectinib
Marketing authorization holder in Denmark	23-09-2019
ATC code	L01XE53
Pharmacotherapeutic group	Antineoplastic Agents
Active substance(s)	Larotrectinib sulfate
Pharmaceutical form(s)	Capsules and oral solution
Mechanism of action	Vitrakvi® is an adenosine triphosphate (ATP) competitive and selective tropomyosin receptor kinase (TRK) inhibitor that was selectively designed to avoid activity with off target kinases. The target for Vitrakvi® is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes, respectively (Vitrakvi® SmPC 2019). In a broad panel of purified enzyme assays, Vitrakvi® inhibited TRKA, TRKB, and TRKC with IC_{50} values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations. In in vitro and in vivo tumour models, Vitrakvi® demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. Vitrakvi® demonstrated potent inhibition of TRK proteins and inhibition of proliferation of tumour cells in a concentration-dependent manner (Vitrakvi® SmPC 2019).
Dosage regimen	*Adults* The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. *Paediatric population* Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Vitrakvi® as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion who, • have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • have no satisfactory treatment options.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Packaging – types, sizes/number of units, and concentrations	Capsules (two pack sizes: 56 capsules a 25mg and 56 capsules a 100mg) and oral solution (100ml a 20 mg/ml)
Orphan drug designation	N/A

2 Abbreviations

ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BOR	Best overall response
BRAF	B-Raf proto-oncogene
BSA	Body surface area
BSC	Best supportive care
CEM	Cost-effectiveness model
CMN	Congenital mesoblastic nephroma
CNS	Central Nevous System
CR	Complete response
CRC	Colorectal cancer
DOR	Duration of response
ECG	Electrocardiography
EMA	European medicines agency
ePAS4	Extended primary analysis set 4 (n=164)
GBM	Glioblastoma multiforme
GIST	Gastrointestinal stromal tumour
GMI	Growth modulation index
HRQoL	Health-related quality-of-life
HSUV	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFS	Infantile fibrosarcoma
INV	Investigator
IRC	Independent review committee
KIT	Tyrosine-protein kinase KIT
LDH	Lactate dehydrogenase
LoE	Loss of exclusivity
LVEF	Left ventricular ejection fraction
MA	Marketing authorization
MASC	Mammary-analogous secretory carcinoma
PMRM	Pooled Model Repeated Measures
MUGA	Multigated acquisition scan
NE	Not estimated/estimable
NR	Not reported/reached
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase receptor
OLS	Ordinary least squares
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Primary analysis set (n=55)
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
QALY	Quality-adjusted life-years
QoL	Quality of life
RANO	Response assessment in neuro-oncology criteria
RECIST	Response Evaluation Criteria in Solid Tumours
SD	Stable disease
SmPC	Summary of product characteristics
STS	Soft-tissue sarcoma
TMB	Tumour mutational burden
TRK	Tropomyosin receptor kinase
TTP	Time to progression

The Economical Application

3 Summary

Vitrakvi® is an orally bioavailable and highly selective TRK inhibitor that provides a rapid and durable outcome for patients with TRK fusion cancer, a rare disease within oncology. The target for Vitrakvi® is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively. It is the first cancer drug to be EMA approved in a histology independent indication.

Vitrakvi® is indicated for the treatment of paediatric and adult patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who

- have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options.

The efficacy and safety of Vitrakvi® in patients with TRK fusion cancer is studied in three multicentre open label and single arm phase I/II trials, which have been pooled to one analysis, summarized as the Vitrakvi® trial. The common denominator across histologies is NTRK-gene fusions. The pooled clinical data demonstrate that Vitrakvi® has rapid, potent, and durable anti-tumour activity across different tumour histologies (Drilon et al 2018, Hyman et al 2019, Hong et al 2020, Data on file 2020).

Results are presented in two data sets being the primary analysis set (PAS) and the extended primary analysis set (ePAS) 4 in short ePAS. The PAS data set contains the first 55 recruited patients of whom all have a follow-up time longer than 24 months. All later on and currently recruited patients are included on the largest data set is represented by ePAS-data. ePAS-data consists of 164 paediatric and adult patients, of whom 55 patients are from the PAS-data.

In the table below the results from the latest data cut off on ePAS5 is show (the data set used in the economic model for base case and the sensitivity analysis). [redacted] For drugs with long term survival and potential cure it takes time to reach median OS for natural reasons. The effect is sustained regardless of tumour site, NTRK-gene fusion type and gene partner.

Paediatric patients (data cut off July 2019) show an even greater ORR and greater survival probability. ORR is 95-100%. In the PAS-data, OS rate at 24-month is 82% for the whole study population and 100% for paediatric patients only. Further, Vitrakvi® shows the ability to be used as a neoadjuvant treatment alternative.

The Vitrakvi® trial is a single-arm multi-centre trial. The lack of a comparator arm is justified. If the study population had been randomized into two treatment arms it would have taken several years before significant OS results could be shown and statistical power could be reached. Clinical practice for patients with a locally advanced, metastatic tumour without a satisfactory anti-tumoural treatment option is BSC in the form of antitumoural treatment. This means last line chemotherapy represented by doxorubicin.

Bayer compares Vitrakvi® to doxorubicin (Judson et al 2014) - a commonly used, efficacious chemotherapy with a well-known safety profile. Furthermore, we consider doxorubicin to be a representative approximation for the supportive care that TRK fusion cancer patients mainly receive. The approach is validated by isolating the non-responders in the Vitrakvi® clinical trial program, assuming their treatment outcomes represent supportive care only, and letting non-responders validate doxorubicin. This is done by running a within study comparison where it is assumed that patients with no response (stable disease and progressive disease) approximate the effectiveness of BSC in the form of doxorubicin. The non-responders arm is further confirmed with results from an intra-patient comparison where PFS on a patient's previous treatment is compared to the PFS of the Vitrakvi® treatment (Von Hoff et al 1998; Italiano et al 2020). Here each patient is their own control minimizing possible confounders due to difference in baseline characteristics between two treatment arms.

A cost analysis is comparing Vitrakvi® with BSC in the form of doxorubicin in Denmark. In the base-case analysis the overall patient population is included meaning both paediatric and adult patients. Paediatric patients have a response rate of 95-100%, why a subgroup analysis in those patients is certainly relevant. Also, a sub-group analysis on adults only has been run.

The cost analysis is based on a cohort state transition model with a mixture cure approach to extrapolate. This model captures the chronic state that is indicated in the Vitrakvi® trial where patients have a long-term survival that is approaching the survival probability for the general population. Assumptions for extrapolation are validated with historical cohorts.

According to the list-prices for Vitrakvi® the incremental costs for Vitrakvi® are 7 104 434 DKK for Vitrakvi® vs doxorubicin. For the paediatric population the incremental costs are 10 129 713 DKK for Vitrakvi® vs doxorubicin. The increased cost for paediatric patients is based on the long-term effectiveness that Vitrakvi® brings where some. Bayer intends to participate in price negotiations with Amgros.

4 Background

Vitrakvi® is a tumour-agnostic cancer treatment, which is a highly selective tropomyosin receptor kinase (TRK) inhibitor that provides a rapid and durable outcome for patients with TRK fusion cancer, a rare disease within oncology. The efficacy results are transformative with a favourable safety profile.

Vitrakvi® received market authorization on September 23, 2019 for the treatment of paediatric and adult patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who

- have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory treatment options.

Vitrakvi® is a highly selective TRK inhibitor. TRK fusion cancer provide a targetable oncogenic driver across multiple solid tumour histologies. Although rare, these pan-cancer kinase fusion events are known to drive tumourigenesis across the multitude of histologies in which they are present. All patients with TRK fusion cancers, no matter the afflicted solid organ, share the same disease mechanism (Stransky 2014, Lange 2018).

TRK fusion cancer is a rare disease with respect to its low frequency. One of the main factors affecting the epidemiology is the low testing frequencies for NTRK gene fusions. The frequency of TRK fusion cancer is reported to be 1.04 in 100 000 people which makes TRK fusion cancer a rare disease, as rare diseases occur in less than 1-2 in 10 000 people (Commission of the European Communities 2008 and Rigshospitalet 2015). Nevertheless, it is now recognized as a disease entity with actionable targets for treatment (Drilon 2018, Kummar 2018). Only in rare cases can NTRK-gene fusion co-exist with other oncogenic drivers of a given cancer. Newly published data show that ALK, BRAF, ERBB2, EGFR, ROS1 or KRAS are unusual in patients with TRK fusion cancer (Bazhenova et al 2020, Rosén et al 2019).

Current treatment modalities for patients with a locally advanced, metastatic tumour without a satisfactory anti-tumoural treatment option is mainly last line chemotherapy mainly doxorubicin. Moreover, all patients included in Vitrakvi® trials have a locally advanced or metastatic solid tumour. They have previously received standard or later-line chemotherapies and have no other satisfactory treatment options available. Thus, Vitrakvi® is aimed at a very specific population with a high unmet medical need.

Vitrakvi® indication is pan-tumour agnostic in a rare cancer based on a data which demonstrated durable efficacy across tumour types. The efficacy and safety of Vitrakvi® in TRK fusion cancer is studied in three multicentre open label and single arm phase I/II trials (LOXO-study, SCOUT-study and NAVIGATE-study), which are pooled into one analysis that will from now on be referred to as the Vitrakvi® trial. The pooled analysis of all three studies is the basis for the approved indication.

5 Patient population, intervention and comparator

A cost analysis has been undertaken based on a model that simulates the long-term effectiveness and costs of Vitrakvi® compared to anti-tumoural BSC as doxorubicin in Denmark. The base case analysis is done on the overall patient population in a mixture cure model. The overall results have been validated using cohorts on similar drugs in the TKI precision medicine family on solid tumours: imatinib and crizotinib. Furthermore, the results in the mixture cure model has been validated using a parametric model in a sensitivity analysis. We have also done a subgroup analysis on the paediatric population in the mixture cure model.

The effect and safety of Vitrakvi® is taken from the Vitrakvi®-trial, which is the pooled analysis of the three multicentre open label and single arm phase I/II trials. The results from the clinical trials have been pooled into one analysis leading to the first data set (**primary data set, PAS**), from July 2020. For a detailed description on the Vitrakvi® trial and clinical results please see the medical application.

The July 2020 data cut-off for the PAS-data has the longest follow-up time and hence allows for differentiation between patient groups that are expected to have a life expectancy similar to the general population and those that do not. The baseline characteristics are similar for patients included in the PAS-data and ePAS-data, see Table 3.

Baseline characteristics for patients in the Vitrakvi® trial

Dataset	PAS	ePAS	PAS Adults only	ePAS Adults only	PAS Paediatrics only	ePAS Paediatrics only
Data cut-off	July 2019	July 2019	July 2019	July 2019	July 2019	July 2019
Total patient population	55	164	43	109	12	55
Median follow-up time. months	31.8	14.5	31.2	14.3	32.8	15.3
Median age, years	45 (range 0.3-76)	42 (0.05-84)	57 (24-76)	56 (19-84)	1.8 (0.33-12)	1.2 (0.05-14)
Number of children, %	21.8	34.2	0	0	100	100
Number of women, %	47	52	47	0.53	50	47
Performance status, %	ECOG	ECOG	ECOG	92	ECOG	ECOG
0 or 1	93.0	86.0	93.0	84.4	92.0	91.0
>=2	7.0	14.0	7.0	15.6	8.0	9.0
≥1 earlier treatment (%)	80	78	79.1	80.7	83.0	74.0
Primary tumour location	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS)	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS), Hepatic, Bone sarcoma, Congenital mesoblastic nephroma, prostate	Appendix, Breast, Cholangiocarcinoma, Colon, GIST, Lung, Melanoma, Pancreas, Salivary gland, Soft tissue sarcoma and Thyroid	Appendix, Bone sarcoma, Breast, Cancer of unknown primary, Cholangiocarcinoma, Colon, GIST, Hepatic, Lung, Melanoma, Prostate, Salivary gland, Soft tissue sarcoma, Thyroid	Infantile fibrosarcoma, soft tissue sarcoma	Melanoma, Soft tissue sarcoma, IFS, Congenital mesoblastic nephroma, Thyroid

NR not reached,
*4 adult patients in ePAS4 were not RECIST assessed 1 died without disease progression, 1 started subsequent cancer therapy and 2 had not yet been assessed post baseline.
In total 2 adult patients in ePAS4 started subsequent cancer therapy.

In the PAS data set, all patients have a follow-up time longer than 24 months. For a more detailed description of the Vitrakvi trial please see the medical application (section 7).

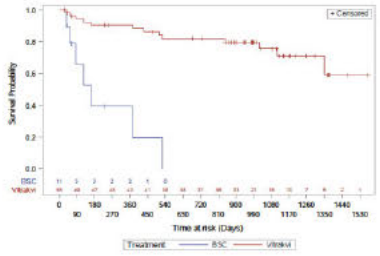
The figures below show that the probability for OS and PFS is consistent at both the 12-month time point, the 24-month and beyond the 36 months follow up point (in the data cut off from July 2020).

[redacted]

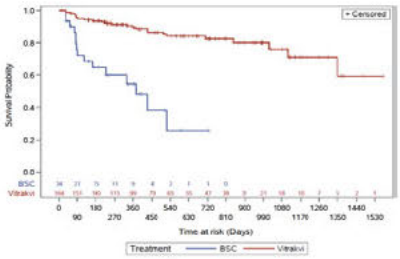
Data cut off July 2019 (PAS-data and ePAS-data)

Data cut off

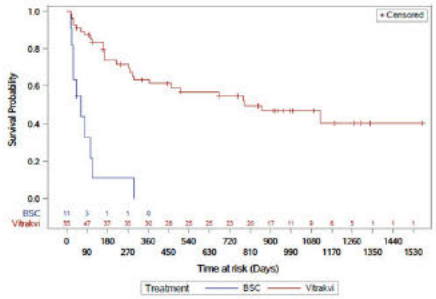
OS-curve for Vitrakvi® and BSC for PAS-data



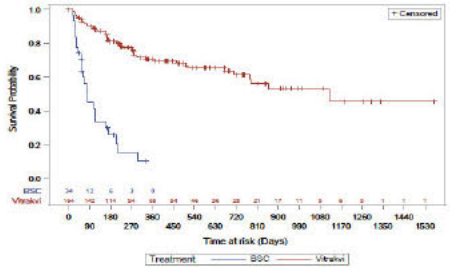
OS-curve for Vitrakvi® and BSC for ePAS-data



PFS-curve for Vitrakvi® and BSC for PAS-data



PFS-curve for Vitrakvi® and BSC for ePAS-data

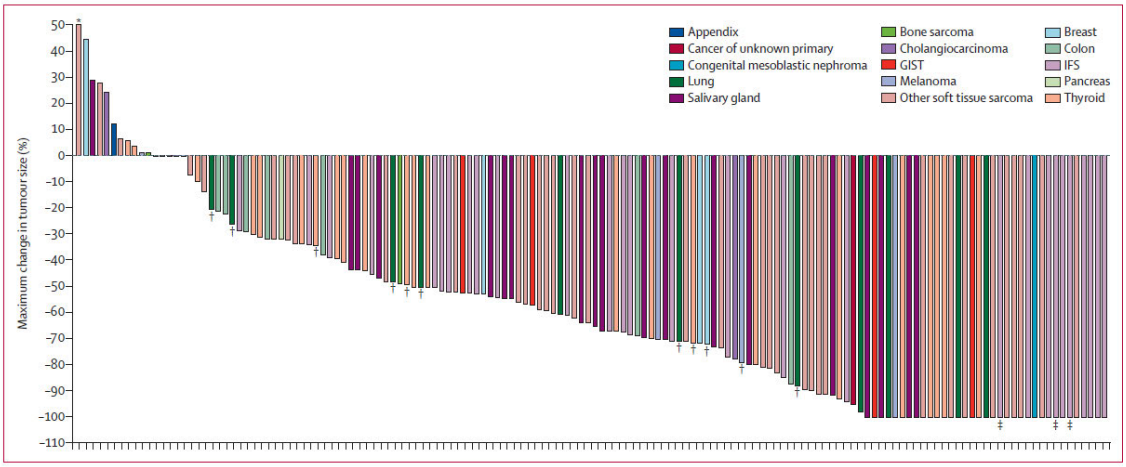


Clinical practice for patients with a locally advanced, metastatic tumour without a satisfactory anti-tumoural treatment option is BSC in the form of doxorubicin/chemotherapy, as a last line antitumoural treatment. A description of the comparator arm is outlined in section 6.2.

5.1 Subgroup analysis

There is no evidence of heterogeneity in treatment effect based on primary diagnosis/tumour type since tumour response does not show any cluster of a specific tumour type as the waterfall plot shows below (ePAS from data cut-off Feb 2019 (Hong et al 2020).

Waterfall plot of the maximum percentage change in tumour size according to tumour type



*Maximum change in tumour size of 93% tumour growth. †Patients with brain metastases. ‡Patients with a pathological complete response.

However, paediatric patients stand out. The efficacy for patients with TRK fusion cancer is specifically strong in paediatric patients with TRK fusion cancer as ORR is greater in paediatrics than in the overall. Also, the probability for survival is greater for paediatric patients.

In the PAS-data (data cut-off: July 2019; n=12) the ORR for paediatric patients is 100% of whom 42% are CR. Furthermore in 3 out of 12 patients' treatment with Vitrakvi® lead to tumour shrinkage to allow surgical removal and patients can discontinue treatment. These patients are here defined as pathological complete responders. In the Vitrakvi® trial some patients are listed as having no other curative options besides amputation or disfiguring surgery. Following treatment with Vitrakvi® surgical treatment has become an option, but with no disfiguring consequences. Patients undergoing these surgeries can reach pathological Complete Response and thus discontinue treatment with Vitrakvi®.

As outlined earlier the effect of Vitrakvi® in paediatric patients is compared to the proxy control arm (consistent of both adult and paediatric patients) and doxorubicin (Judson et al 2014). Almost all paediatric patients respond to treatment with Vitrakvi®, which is why the group of non-responders for paediatric patients is too small to create their own Proxy-control arm BSC (0% and 10% in the PAS and ePAS data respectively).

The adult curve for doxorubicin and the Proxy-control arm BSC are applicable to paediatric patients who present with locally advanced unresectable disease, where Vitrakvi® is indicated. Paediatric patients are, generally speaking, doing very well on first-line chemotherapy treatment, but paediatric patients who have received several lines of treatment, and/or for whom no other suitable treatment is available, are deteriorating quickly. Hence, Bayer use the Proxy-control arm BSC for the entire patient population as a comparison arm among paediatric patients.

In order to minimize possible uncertainties and objections on that matter we have two models comparing the effectiveness Vitrakvi® in paediatric patients to

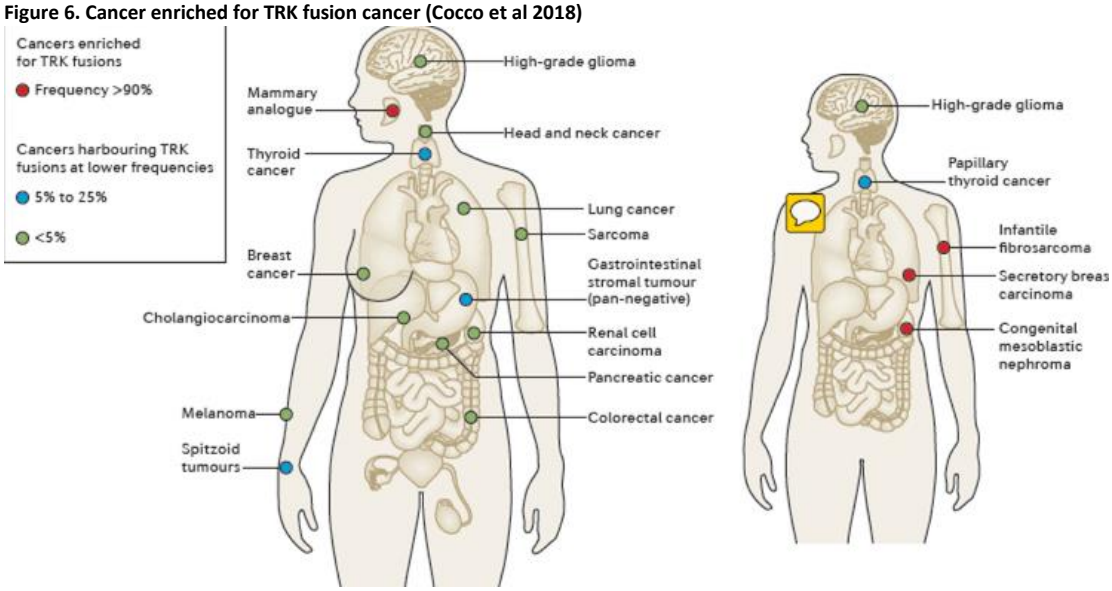
- paediatric patients with no treatment alternatives other than mutilating surgery
- paediatric patients with relapsed or progressed solid tumours.

Further subgroup analyses are

- adults only
- adults with low frequency (<5%) of TRK fusion cancer (categorized to Cocco et al 2018) and
- adults and paediatric patients with high frequency (>90) TRK fusion cancer (categorized to Cocco et al 2018).

The pattern of testing for TRK fusion cancer differs in high and low frequency cancer. In the tumour types with a high frequency of TRK fusion cancer, testing is more common since the occurrence is so high. Also, broader testing panels are used covering several oncogenic drivers. Testing costs are therefore only included in the scenario analysis with tumour types with a low frequency of NTRK gene fusion, where testing for oncogenic drives is not as common.

Figure 6. Cancer enriched for TRK fusion cancer (Cocco et al 2018)



6 Cost analysis

The cost model is a cohort state transition model with a mixture cure approach for extrapolation. This technique is appropriate in capturing progressive chronic conditions that are described with clinical outcomes requiring an ongoing, time-dependent risk, such as progression or death. Furthermore, mixture cure extrapolation is appropriate where survival curves indicate two patient populations demonstrating a plateau and indicating a heterogenous patient population in regard to risk of progression and death: One with short and one with long-term survival.

In a cohort state transition model, the number of patients in each health state is derived from the PFS and OS curves for each treatment.

The model includes the health states: Progression-free, Progressed and Death, see Figure 7.

Model structure for Vitrakvi® compared to BSC as doxorubicin

Within each cycle of the model, patients can either:
- Stay in their current health state
- Move to progressive disease (from the progression-free health state)
- Move to death (from either progression-free or progressed disease health states)

The proportion of patients in the progression-free health state is equal to the survival function value for PFS, while the proportion of patients in the dead health state is equal to 1 less the survival function value for OS. Lastly, the proportion of patients in the progressed health state is equal to the survival function of OS – PFS.

The included estimation on resource use is based on estimations from two clinical active oncologist. Cost variables are taken from Danish price lists.

6.1 The Vitrakvi®-arm

In each cycle of the model, patients treated with Vitrakvi® are assigned to one of three mutually exclusive health states according to the proportion of patients who are “progression-free”, “progressed”, or “dead” (Figure 7). [redacted] After the observed data, KM-curves are transitioned to extrapolation. This is the latest point available from the clinical trial.

Mixture cure models are superior to other models when the patient population is heterogeneous in the sense that some patients are "long-term survivors" while other patients progress rapidly. As such, in the context of this economic evaluation, "long-term survivors" are to be understood as those patients expected to achieve long-lasting benefits from receiving the active substance whose risk of death is the same as that of a disease-free person, and "non-cured" is to be understood as those who are not expected to derive such benefits (Othus et al 2017).

Patients with a long-term survival are included in the cured group and patients with a shorter survival probability in the non-cured group.

- **Patients in the cured group so called long-term survivors:** are defined as patients treated with Vitrakvi® that achieve a CR or PR with a duration of response (DoR) longer or equal to 24 months as well as patients that discontinue treatment due to surgical resection, so called patients with **pathological complete response** who experience a tumour shrinkage through treatment with Vitrakvi® to such a degree that the tumour can be surgically removed. Hence, patients can stop treatment and are viewed as potentially cured. Those patients can be assumed to have an almost similar live expectancy as the general population (Othus et al 2017).

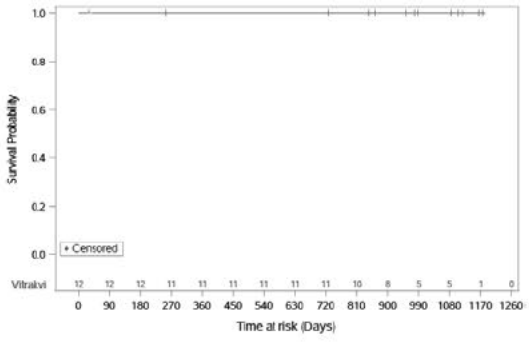
- **Patients in the non-cured group** are defined as patients with an increased risk for progression and death. This group is comprised of the remaining patients, i.e. patients with a SD, PD or CR and/or PR with a DoR≤24 months.

The fact that there is a proportion of long-term survivors and pathologically complete responders in the population in PAS-data and in ePAS-data (July 2020) is shown graphically with a plateau phase in the OS graph for Vitrakvi®, see Figures 8 to 11 below.

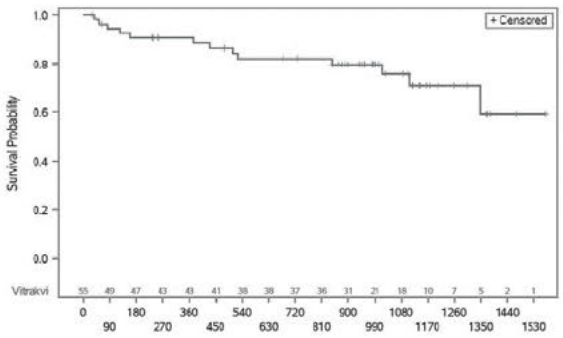
[redacted]

OS-data for pediatric- and overall population, data cut off July 2019 (PAS-data and ePAS data)

OS for paediatric patients with TRK-fusion cancer (n=12, PAS-data)

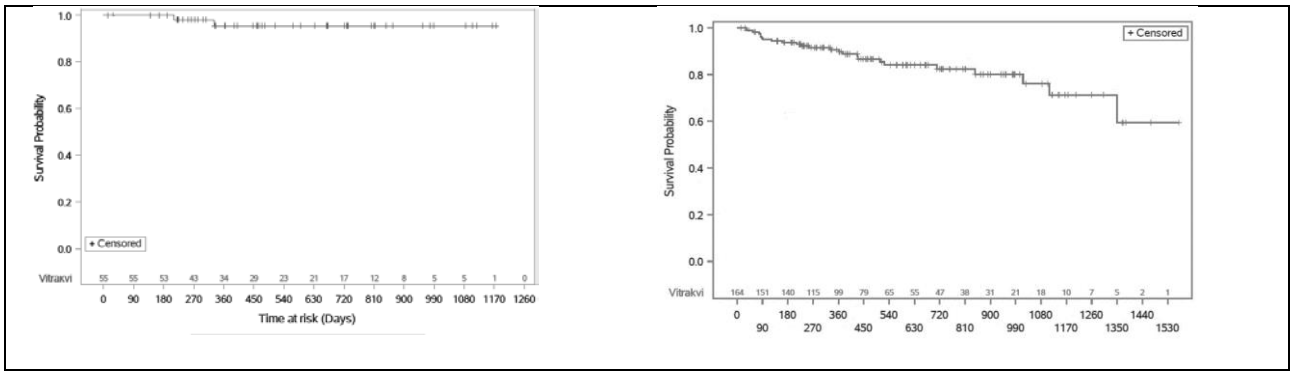


OS for the overall TRK-fusion population (n=55, PAS-data)



OS for paediatric patients with TRK-fusion cancer (n=55, ePAS-data)

OS for the overall TRK-fusion population (n=164, ePAS-data)



The definition that we use at present as an estimate of the proportion of patients expected to be in the long-term survivor's group are patients with CR or PR with DoR ≥ 24 months and/or surgical resection. Clinical experts, contacted by Bayer, confirm that this definition can be used as an approximation for long-term survivors given that follow-up is taking place. This group of patients continues in the progression-free health stage.

In the base-case scenario 36.2% of patients are included in the long-term survivor's group [redacted] according to the definition above. Included in this group are 5,5% patient with pathological complete response (surgical cured) – i.e. potentially cured, see Table x below.

[redacted]

6.2 The comparator-arm

Clinical practice for patients with a locally advanced, metastatic tumour without a satisfactory anti-tumoral treatment option is BSC in the form of doxorubicin as a last line chemotherapy. Doxorubicin can be used as a representative for other chemo therapies, both in mono and in combination since there is no evidence supporting a difference in effect between different chemotherapies or combinations. Chemotherapies in combinations are thus not more effective compared to doxorubicin, but more expensive. The patients tolerability is the driving factor for giving different types of chemotherapies in this setting for solid tumours. This treatment modality is in line with the Vitrakvi® protocol developed by the Medicine Council.

The effect of Vitrakvi® is studied in a single arm trial because,

- TRK fusion cancer is a rare disease. If patients would have been randomized to two treatment arms (one active arm being Vitrakvi® and a comparator arm being doxorubicin) this would have resulted in poor statistical power. A randomized trial would lead to either a low number of patients in each arm or an extremely long period of inclusion and follow-up time.

- A single arm trial design avoids confounded OS results due to expected cross over since Vitrakvi® is a precision medicine that if compared to doxorubicin would show significant OS and leaving patients in the comparator arm would be unethical.

In order to bridge possible uncertainties combined with a single arm trial, the comparator arm is validated with another possible comparator alternative being the Proxy-control arm BSC and the intra-patient comparison GMI.

6.2.1 Doxorubicin

Patients with TRK fusion cancer that have metastasis, local advanced cancer or are not eligible for surgery are most likely be treated with chemotherapy such as doxorubicin.

Doxorubicin is used in a wide range of histologies. An identified article in the literature review is Judson et al (2014), which is mostly relevant as soft-tissue sarcoma (STS) is the most frequent tumour histology in the Vitrakvi® trial (20% in the PAS-data) and has available long-term efficacy data.

Long-term data on doxorubicin used in the model is taken from Judson et al 2014, which evaluates the effect of doxorubicin on PFS and OS in patients with advanced or metastatic STS as first line treatment. The study is a randomized phase III trial that includes 455 patients. Patients are randomized into the respective treatment arm: doxorubicin in combination with ifosfamide compared to doxorubicin alone. The median follow-up time is 56 months (4.7 years). Median age in the doxorubicin group is 48 years. The proportion of women is 55%. 43% have a WHO performance status higher than 1. The median OS for the doxorubicin arm is 12.8 months (95.5% CI: 10.5-14.3) and the median PFS 4.6 months (95.5% CI: 2.9-5.6), see Table 5 below.

The doxorubicin arm is validated with the anti-tumoural BSC represented by non-responders to Vitrakvi®. The respective arm validates each other and hence really do represent BSC. As is outlined in the medical section, an intra-patient comparison has been conducted where each patient is their own control. Results from the intra patient comparison analysis validate the Proxy-control arm BSC and doxorubicin arm when comparing the Time to progression on previous therapy for patients with TRK fusion cancer to PFS with doxorubicin and BSC.

Background characteristics and outcomes of doxorubicin in STS (Judson 2014)

Publication	Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial (Judson et al 2014)
Population	Adult patients with high-grade soft-tissue sarcoma with unresectable or metastatic disease progression within 6 weeks before treatment
N	228
Follow-up, months, median	56.4
Age, years, median	48 (range 18-60)
Paediatric, %	0
Female, %	55
Performance status, %	WHO
0 or 1	100
>=2	<1
At least one previous systemic therapy (%)	NR
CR, %	<1
PR, %	13
Site of active disease	Different soft tissue sarcoma types: undifferentiated pleomorphic sarcoma, myxoid or round cell liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, synovial sarcoma, myxofibrosarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumour, epithelioid sarcoma, unclassified high-grade sarcoma (not otherwise specified))

NR=not reached/not reported, NE=not estimable, INV=investigator assessed (RECIST)

6.2.2 Doxorubicin overlaps with the Proxy-control arm BSC

As there is a lack of evidence on treatment effects of other therapies in TRK fusion cancer a within-study comparison can be undertaken where non-responders represent patients with a treatment effect equivalent to patients having been treated with anti-tumoural BSC.

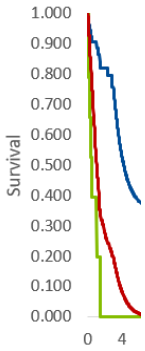
Patients achieving a response as stable disease (SD) and progressed disease (PD) in the Vitrakvi® trial (PAS-data) are defined as non-responders. The inherent assumption here is, while exposed to Vitrakvi®, patients do not register a treatment response and therefore are not assumed to be exposed to a treatment effect. This is a conservative approach, as any patient being administered an active substance, and especially those not progressing (SD), certainly receive more benefit than if not given any active treatment. Background characteristics are outlined in Table 6.

Background characteristics and outcomes of non-responders in PAS (data cut-off July 2019)

Analysis set	BSC
Population	Non-responders of PAS July 2019 (=INV assessed as SD and PD)
N	11
Follow-up, months, median	2.8
Age, years, median	43 (24-74)
Paediatric, %	0
Female, %	73
Performance status, %	ECOG
0 or 1	82
>=2	18
At least one previous systemic therapy (%)	91
Primary tumour location	Cholangiocarcinoma, Salivary gland, Soft tissue sarcoma, Melanoma, Colon, Melanoma, Breast, Appendix, Salivary gland, Lung

Figure 12 below shows that the efficacy for the BSC-arm (OS-data from PAS for non-responders) overlaps with doxorubicin. The BSC-arm is hence acting like a real control-arm would have done when BSC would have been given as doxorubicin. The possible uncertainties attached to a single-arm study design are thereby minimized. For simplicity reasons we call this a Proxy-control arm BSC.

OS-graph for doxorubicin (Judson et al 2014) overlaps with the Proxy-control arm BSC (non-responders from PAS-data)



Source: Cost analysis and Judson et al 2014

The Proxy-control arm validates the long-term data for doxorubicin by Judson et al (2014) and the GMI curve (outlined in section 6.2.3.), which lies a bit higher than the Proxy-control-arm. Thus, a comparison versus doxorubicin is a conservative comparison, both from a relative effect perspective, and from a health economic perspective as well as a budget impact perspective:

- The curve closest to our Vitrakvi® arm produce the smallest "area under the curve" between the Vitrakvi® arm and the comparator arm

Doxorubicin is the comparator lying closest to our Vitrakvi®arm – and thus produces the smallest area under the curve from all perspectives mentioned.

6.2.3 Validation of the comparator arm with the GMI-index

Bayer has conducted an intra-patient comparison utilizing the innovative approach introduced by Von Hoff - the Growth Modulation Index (GMI). A self-comparison means the patient is controlled in terms of demographic factors and to a large extent clinical factors, with disease stage expected to decline over time making the analysis conservative with a bias against the later line treatment. Self-comparisons are highly relevant from a clinical perspective.

The PFS curve for the comparator arms can be validated using the intra-patient comparison. From the Growth Modulation Index (GMI) developed by Von Hoff (1998), Bayer has compared:

- PFS for patients treated with Vitrakvi®
- Time to progression (TTP) for the same patients compared with the previous treatment they received before initiating Vitrakvi®.

Plotting the TTP provides another estimate of the natural history of TRK fusion cancer patients when treated with current standard therapy. The TTP shows how the effect should have been in a comparator arm with anti-tumoural treatment alternative such as doxorubicin if it would have been included in the Vitrakvi® trial.

This analysis is performed on the 164 patients (ePAS, data cut-off July 2019) including patients who have at least one prior therapy in any setting (122 patients).

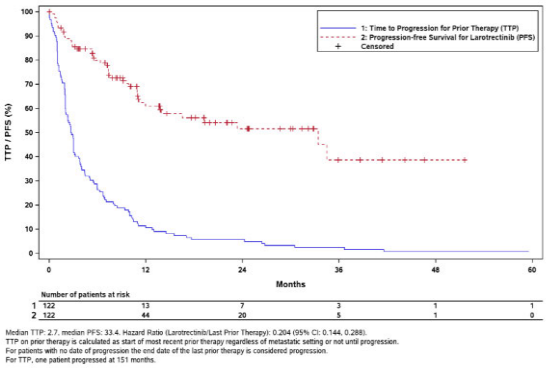
Comparing the PFS-curves for the Proxy-control-arm and the GMI-arm in Figure 13 and 14 below we see that the hypothesis if patients in the proxy-control arm really match the GMI-arm is proven and that the proxy-control-arm can be viewed as a realistic control arm.

The hypothesis if patients in comparator arms match the GMI-arm and if thus the comparator arms can be viewed as a realistic control arm, the PFS-curves for the comparator arms and the GMI-arm in the figures below can be compared.

- At 12 months follow up: In all arms the probability of being progression free is between 12% to 15%
- At 24 months follow up: In all arms the probability of being progression free is between 8% to 10%
- At 48 months follow up: It is important to note that some patients are censored, namely those patients with CR and PR who has a shorter follow time than 24 months. Those patients can turn out to be long term survivors at later data cuts. For now, the probability in all arms of being progression free is 0%

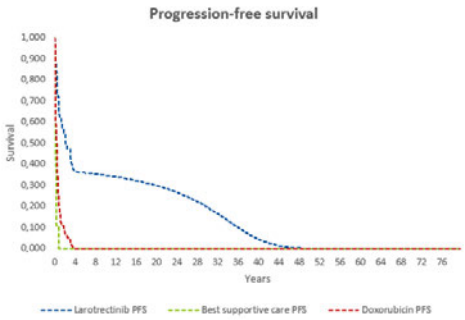
To assess cost efficiency, the difference over time between the extrapolated curves is crucial. Since differences are marginal over a short period of time, Bayer believes that these sources validate each other and thus provide a probable assessment for the cost-analysis.

Kaplan Meier Figure – Time to progression on previous treatment (blue) and PFS for Vitrakvi® (red)



Median TTP: 2.7, median PFS: 33.4. Hazard Ratio (Larotrectinib/Last Prior Therapy): 0.204 (95% CI: 0.144, 0.288).
TTP on prior therapy is calculated as start of most recent prior therapy regardless of metastatic setting or not until progression.
For patients with no date of progression the end date of the last prior therapy is considered progression.
For TTP, one patient progressed at 151 months.

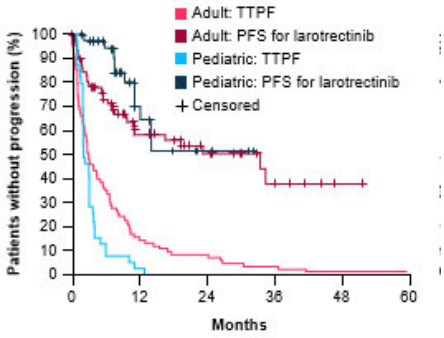
Extrapolated weighted PFS curve for TRK-fusion cancer patients treated with Vitrakvi® (blue), BSC and doxorubicin (green and red)



As outlined previously the Proxy-control arm is also applied in the paediatric analysis since almost all paediatric patients respond to Vitrakvi®. Recently an intra-patient comparison on paediatric patients have been run and presented at ESMO. Figure 16 shows the intra-patient comparison for adults (n=83) and paediatrics (n=39) separately. The HR for adults is HR 0.27 (0.18-0.40) and for paediatrics HR 0.07 (0.03-0.16), showing that there is a significant reduced risk for progression for both adults and paediatric patients (Italiano et al 2020).

The light red line (Adult TTPF) is the same line as we see in Figure 13 (blue line). Below it is shown that paediatric patients have a shorter progression free survival on their previous treatment than is the case for adults. Thus, applying the doxorubicin arm as a comparator arm in the paediatric scenario is a conservative assumption.

Intra-patient comparison: PFS-graph for Vitrakvi® (adults=dark red; paediatrics = dark blue) and time to progression for the same patients on their previous treatment (adults= red; paediatrics = light blue) (ePAS, July 2019) (Ref: Italiano et al 2020)



	Adult		Pediatric	
Median, months (95% CI)	3.0 (2.3, 5.1)	33.4 (10.9, NE)	2.0 (2.0, 3.0)	NR
HR (95% CI)	0.27 (0.18, 0.40)		0.07 (0.03, 0.16)	

6.3 Extrapolation of treatment effects

As previously described, patients follow the OS and PFS curves from the Vitrakvi® trial [redacted] the data cut-off in July 2019. Thereafter, the patients are divided into two groups: long-term survivors and non-cured. This point in time is referred to as the Mixture Cure Model transition point (MCM transition point). We use the same MCM transition point for the Vitrakvi® arm and the comparator arm.

After the MCM transition point, OS and PFS curves are extrapolated for the long-term survivors and non-cured population separately by applying relative risks RR versus the background mortality. In the figure below the black dotted line represents the background mortality of the normal population.

OS and PFS on the Overall patient population

Judson et al. (2014) Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncology, 15: 415-23.
Guyot et al. (2012) Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology, 12:9.
WebPlotDigitizer. [Online]. Available: https://apps.automeris.io/wpd/. [Accessed: 2020-08-27].
Wei & Royston (2017) Reconstructing time-to-event data from published Kaplan–Meier curves. Stata Journal, 17(4): 786–802.

- Survival curves for patients with long-term survival is compared to the normal population 1.5 (RR) for adults and to 1.0 (RR) for paediatrics. The age-adjusted and weighted RR applied to the entire cured group is estimated at 1.39:

$$1.39 = 1.0*22\%_{\text{Paediatrics}} + 1.5*78\%_{\text{Adults}}$$

  - **Long-term survivors in the Vitrakvi® arm:** 36.4% of the patients are included in the long-term survivors group (CR and PR with a DoE ≥ 24 months) after [redacted] 5.5% of patients have achieved pathological complete response and have the potential to be cured including patients with long-term survival.

  - **Long-term survivors in the control arm:** The proportion of long-term survivors and patients with potential cure has been set to zero in the comparison arms, as it is highly unlikely that patients treated with BSC in the form of doxorubicin will have survival benefits like the normal population based on the results for doxorubicin in Judson et al 2014 with <1% of the patients reaching CR and 13% reaching PR with a median follow-up time of 56 months.

    The mechanism of action for doxorubicin does not show a rational that there would be long-term effects for doxorubicin. Furthermore, median PFS in Judson et al 2014 is only 4.6 months (95% CI: 2.9-5.6 months). In the model, however, it is possible to set different proportions of patients in the long-term survivors group even in the comparison arm as scenario analysis.

- Survival curves for the non-cured population are adjusted to match the median survival of patients on doxorubicin in Judson (2014) (OS 12.7 months; PFS 4.6 months). This calibrates to a RR of 341 for OS and 950 for PFS. In the paediatric sub-group analysis the same RR are applied.
  Hence, Kaplan-Meier data for doxorubicin where recreated from Judson et al (2014) using the WebPlotDigitizer according to the method developed by Wei et al (2917) and Guyot et al (2012). In short this means the survival data from the original figure can be extracted.

  Patients with no long-term survival is given an RR that is calibrated to be constant in relation to observed OS and PFS data in patients treated with doxorubicin in Judson et al 2014 (OS = 341 and PFS = 950). That means that the PFS and OS curve are adjusted to match the median OS of patients on doxorubicin in Judson (2014) being 12.7 months and median PFS being 4.6 months.

As previously outlined this approach is validated with the intra-patient comparison, showing the PFS on the previous treatment before Vitrakvi®, see section 6.2.3. in the economic part of the application.

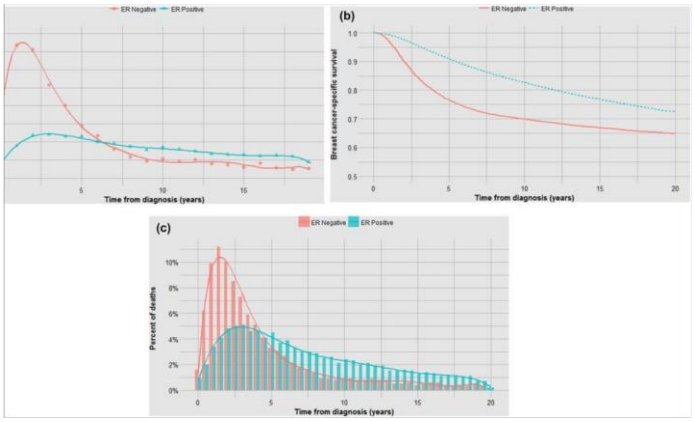
The assumption of long-term survival can be applied, as is done here, on patients with a CR and PR response with a DoR response equal or longer to 24 months.

A 2-year response rate is a milestone for that the current treatment is working and that there is an increased probability for long-term survival. Patients remain however on follow-up as a 5-year survival is the second mile stone for determining long-term survival, the probability of the patients being long-term survivors increases even further that the patients are long term survivors. Currently we do not have data on 5-year survival. The 2-year survival is however a first indicator. We are happy to submit follow-up data later on. We would like to clarify our previous example.

In breast cancer relapse occurs during the first 2-5 years but with different dynamics. For breast cancer this is shown through the ER status.

The yearly death rate for patients can be predicted by the likelihood of the adjuvant treatment to eliminate all metastases and distribution of deaths over time see below the OS curve for breast cancer divided by subgroup population (ER-positive, ER-negative breast cancer) (Narod et al 2018).

Impact of ER status on annual mortality rates. Impact of ER status on actuarial survival. Impact of ER status on time to death.



First of all, the figure above shows that breast cancer is not a homogenous disease: Patients with the markers ER+ and ER- are not similar and need different treatments. Secondly, the mortality risk is highest for both ER+ and ER- before 5 years. The peak is at 2-3 years and flattens out thereafter and becomes fairly stable over time. The mortality risk peaks for both ER+ and ER- before the 2-years follow up. Thereafter it is flattened out and becomes stable.

The above figure is thus showing an illustrative way that the 2-years survival can predict long term survival. Note that we assume an increased risk for progression or death of 50% for adults in order to have a more conservative assumption.

To create a Vitrakvi® arm after the study period, the curves for patients in the group long-term survivors and non-cured respectively are weighted together based on their relative proportion, whereby composite curves for the OS and PFS are generated for a Vitrakvi® arm. See Figures 18 and 19 below. To validate the assumption of long-term survival, the weighted Vitrakvi® arm is compared with historical cohorts being imatinib and Xalkori® (see section 6.4.1.)

[redacted]

6.4 Validation of the extrapolation method

6.4.1 Validation of the extrapolation of the Vitrakvi® arm after at data cut-off - with historical cohorts and sensitivity analysis with parametric model

The weighted Vitrakvi arm is validated with historical cohorts. Thereby the extrapolated OS and PFS curve are validated with historical cohorts:

- Casali et al 2017: imatinib within advanced cKIT-positiv GIST
- Solomon et al 2018: Xalkori® within ALK-positive advanced nonsquamous NSCLC

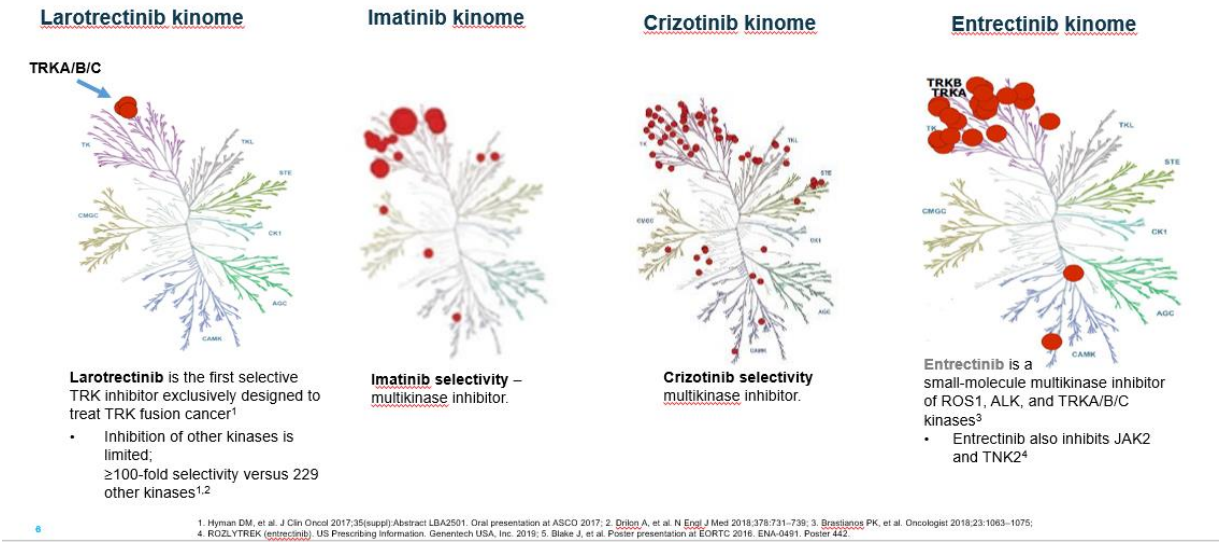
Vitrakvi® is a tumour agnostic treatment alternative for a specific oncogene. The best alternative for validation would be with another precision medicine meaning a treatment alternative that inhibits tyrosine kinases or a so called TKI-inhibitors. Tyrosine kinases are enzymes that activate signal transmission cascades and thus regulates various cell functions, such as cell signaling, survival and growth. Imatinib is the first TKI inhibitor approved for human therapy. Imatinibs mechanism to inhibit important signaling pathways for certain cancers, and its history of approval, efficacy and safety have become paradigmatic in the whole field of targeted drugs.

Imatinib is a selective TKI inhibitor of ABL, ARG, KIT, PDGFR, and certain oncogenic forms, especially BCR-ABL. The drug has been a breakthrough in the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal (GIST) tumours by inhibiting a cancer-producing mechanism.

Xalkori® (crizotinib) is also a TKI inhibitor, with high affinity for ALK and ROS1 tyrosine kinases, and with lower affinity for several other different tyrosine kinases, including TRK fusion cancer. Xalkori® has a narrower indication, and is currently approved for treatment in first-line treatment of adults with anaplastic lymphoma kinase (ALK) -positive advanced non-small cell lung cancer (NSCLC), for treatment of adults with previously treated anaplastic lymphoma kinase (ALK) -positive advanced non-small cell lung cancer (NSCLC), for the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC). Xalkori® has drastically improved the survival chances of these patient groups (Solomon et al 2018).

Vitrakvi®, imatinib and Xalkori® thus belong to the same class of drugs. Vitrakvi® does however inhibits more specifically and inhibits tumour agnostics. The figure below shows the kinome for Vitrakvi®, imatinib crizotinib and entrectinib.

Tyrosine kinase dendrogram which shows kinomen for Vitrakvi, imatinib, crizotinib and entrectinib. The red dots indicate the inhibitation.



As such, it is reasonable to utilize these therapies targeting oncogenic drivers in solid tumours to inform the extrapolation of Vitrakvi®. The publications are selected based on the criterion that these have a study population with similar baseline characteristics as patients in the Vitrakvi® study (Casali 2017, Drilon 2018, Hyman 2019, Solomon 2018). Both studies are first line treatment options. In addition, the follow-up time is relatively long for both Xalkori® and imatinib.

Overview of the effect of Xalkori® (Solomon 2018)

The effect for Xalkori® is taken from the long-term study from Solomon (2018). The study compares Xalkori® with chemotherapy. Patients who progress on chemotherapy can switch to the Xalkori® arm. Table 7 shows baseline characteristics of patients treated with Xalkori®. No children are included in the study. At a median follow-up period of 46 months (3.8 years), HR for the OS is 0.760 (CI: 0.548-1.053). 144 of 171 patients in the chemotherapy arm received Xalkori® as subsequent treatment. When adjusting for cross-over, HR for OS is 0.346 (Bootstrap CI: 0.081-0.718). The median OS is achieved when adjusted for cross-over and is 59.8 (44.6 to NR). The median PFS is 10.9 (CI 8.3–13.9) months. See the table below.

Overview of the effect of imatinib (Casali 2017)

The effect of imatinib is taken from the long-term study from Casali (2017). The effect of imatinib in advanced cKIT-positive GIST has been studied in a follow-up study of approximately 10 years. The study compares imatinib (400 mg daily) with a higher dose of imatinib (800 mg daily). Patients who progress on the standard dose may switch to the second treatment arm. 946 patients are included in the study. The effects for each dose are similar. Also, worth mentioning is that the study presents a multivariate regression analysis that shows that KIT mutation and the size of the lesions are significant prognostic factors for the probability of survival for more than 10 years. The median OS is 46.8 (CI 39.6–52.8) months and the median PFS 14.9 (CI 11.8–17.7) months. Note that the table below shows the OS data for Xalkori® adjusted for cross-over.

Comparison of imatinib, Xalkori® and Vitrakvi®

Publication/Analysis set	Imatinib (Casali et al 2017)	Xalkori® (Solomon et al 2018)	Vitrakvi® PAS
Population	Advanced or metastatic c-KIT positive GIST(400mg)	ALK-positive advanced nonsquamous NSCLC	July 2019
N	473	172	55
Follow-up in study, OS, years, median	10.9	3.8	2.6
Age, years, median	60 (IQR 49-67)	52 (range et al 22-76)	45 (range 0.3-76)
Paediatric, %	NR	NR	22
Female, %	40.2	60	47
Performance status, %	WHO	ECOG	ECOG
0 or 1	86	94	93
>=2	14	6	7
At least one previous systemic therapy (%)	33	Studied in first line	80
CR, %	7	2	24
PR, %	44	73	56
mOS, months	46.8 (39.6-52.8)	59.8 (CI 46.6-NR) (adjusted for crossover)	Not reached
mPFS, months	20.4 (CI 18.0-24.0)	10.9 (CI 8.3-13.9)	25.8 (CI:9.9-NE)
Site of active disease (%)/Primary tumour location	GI (31.7), liver (68.7), lymph node (10.4), lung (8.7), bone (1.5), skin (1.5), brain (0.2)	lung (adenocarcinoma and non-), brain metastases, bone metastases	Lung, Salivary gland, Soft tissue sarcoma, GIST, Thyroid, Appendix, Colon, Breast, Melanoma, Cholangiocarcinoma, Pancreas, Infantile fibrosarcoma (IFS)

To validate composite OS and PFS of Vitrakvi®, observed OS and PFS data are compared to imatinib and Xalkori® in a naive comparison, observed differences in patient characteristics and differences in efficacy must be considered:

1. median OS has not been reached for Vitrakvi®

2. Median PFS has been achieved throughout the patient population and is longer than that of imatinib and Xalkori®. Since the patients in the Vitrakvi® study are followed up for over 30 months with median PFS of 25.8 months with more patients in CR and patients with pathologically complete response that has the potential to be cured, there is reason to assume that median OS will be at least as long as for imatinib and Xalkori®

3. In the Vitrakvi® trial, younger patients are included compared to both the imatinib and Xalkori® studies, which is likely to lead to even longer median OS compared to the historical controls. Existing diagnostic infrastructure is likely to initially identify more children than adults with TRK fusion cancer in Denmark.

4. More patients in the Vitrakvi® study have received prior systemic treatments compared to both imatinib and Xalkori®.

To summarize, Bayer finds it relevant to utilize these studies for validation as both therapies:

- are targeted kinase inhibitors with few off-target effects
- target molecularly defined disease with disease expression in a diverse range of histologies
- have studies with relatively long follow-up periods

- have studies with relatively similar baseline patient characteristics as the Vitrakvi® study

Vitrakvi total patient population contains also paediatric patients whilst Crizotinib and Imatinib only contains adult patients. We have placed the OS curve in base case for Vitrakvi in between Crizotinib and Imatinib even though the overall OS curve for Vitrakvi with high probability lies above the Crizotinib curve.

In the mixture cure model for patients reaching long-term survival on Vitrakvi® it is assumed that paediatrics have a survival risk similar to the general population meanwhile adults have an increased risk for an event (progression or death) with a 50% increase compared to the general population. We have submitted evidence showing that 2-years survival can predict long term survival.

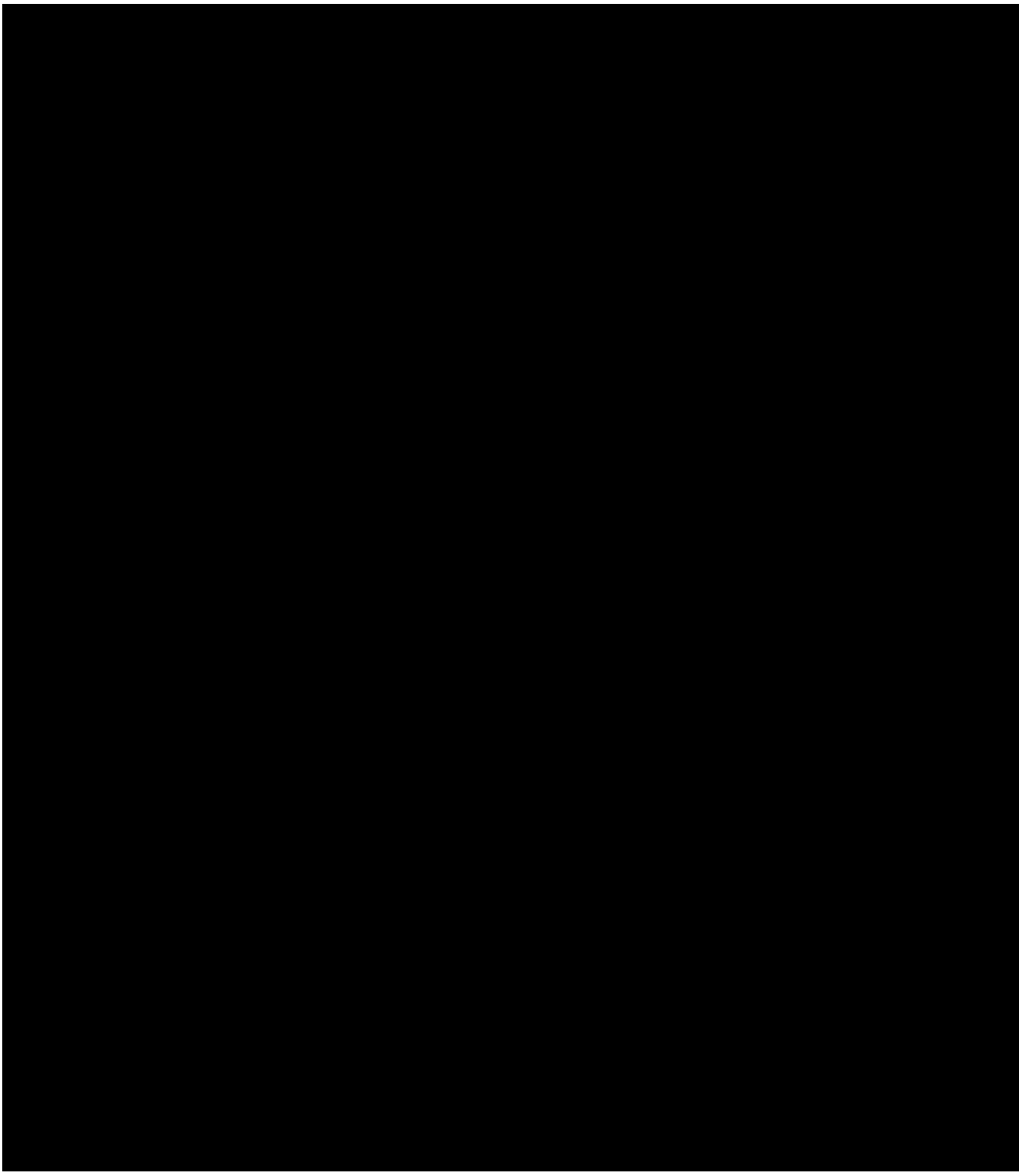
However, we would like to show yet another way of validating the estimated long term OS-curve for Vitrakvi by comparing the survival curves of

- the cohort state transition model with a mixture cure approach for extrapolation (the model submitted to Medicine Council)
- the partition survival model with parametric survival curves for extrapolation.

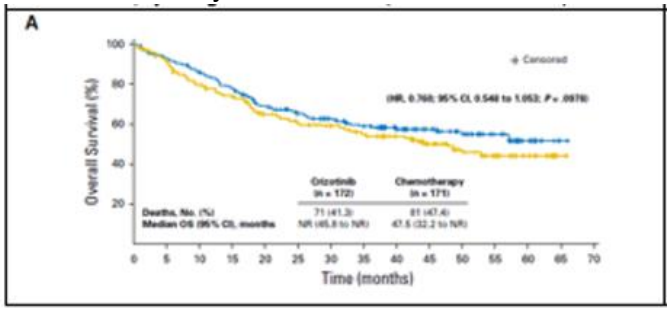
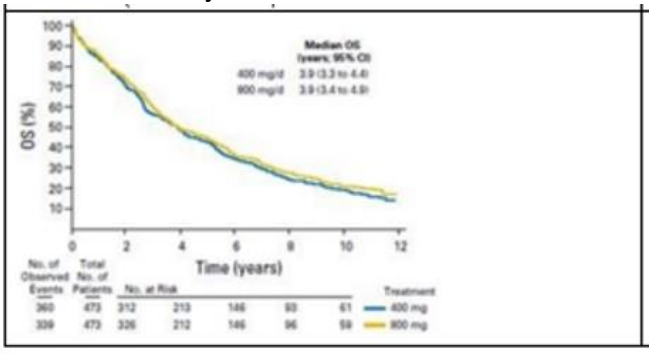
Even if the partition survival model is populated with data from [redacted] (cost and background mortality) **the survival curves that the two models generate respectively can be used for validation of each other**. Thereby we validate the RR applied in the cohort state transition model with a mixture cure approach.

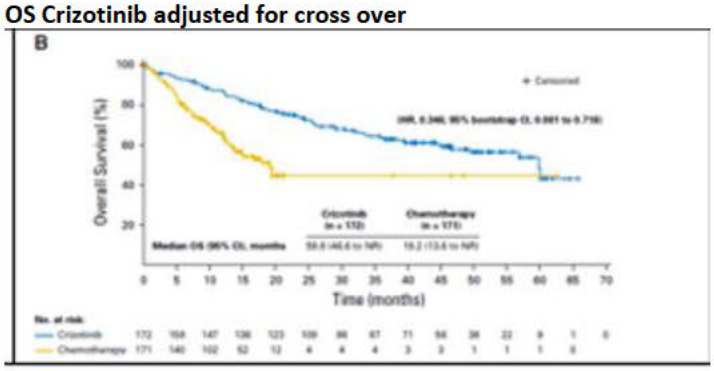
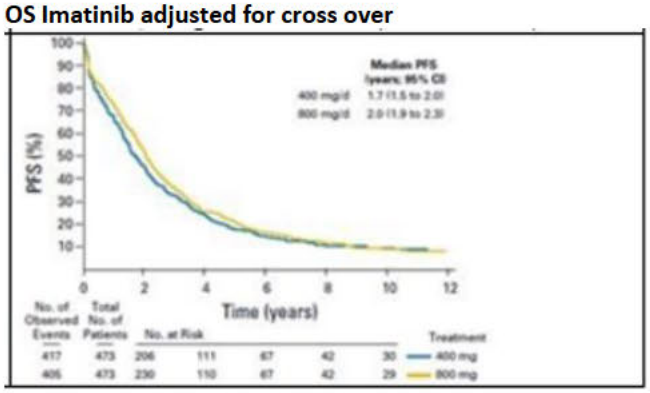
The model includes all fitted standard parametric curves: Exponential, log-normal, log-logistic, Gompertz, Weibull and generalized gamma were considered, compared and assessed using the goodness-of-fit criteria by applying the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Smaller AIC/BIC values indicate a better statistical fit. Models with a difference in AIC and BIC of less than 5 are assumed to be of equal statistical fit.

[1] Where patients with long-term survival have a RR for OS and PFS of 1.39 (1.5 (RR) for adults and to 1.0 (RR))



[redacted]

Crizotinib and Imatinib references	
OS Crizotinib not adjusted for cross over	**OS Imatinib not adjusted for corss over**
	

OS Crizotinib adjusted for cross over	OS Imatinib adjusted for cross over
	

Vitrakvi® is a long-term treatment. Thus, as survival is decreasing, treatment costs decrease. As we see with an increasing RR for PFS and OS the incremental costs decreases.

Mixture cure models can capture long-survival. Our base case model allows for RR to be changed, and hence is very dynamic as we see above. [redacted] We believe this difference should be justified by the fact that more children are being included in the Vitrakvi® arm as well as more patients reach a CR in the Vitrakvi® trial than is the case for imatinib.

6.4.2 Model cycle

The model uses a cycle length of one week.

6.4.3 Adverse events

Adverse reactions of grade 3 and 4 are cost driving adverse events. Adverse reactions with a frequency equal to or greater than 5% have been given priority. We have assumed that incremental differences in side effects between the drugs occur only when the patients receive active treatment in accordance with the treatment termination curves. Table 9 below present the adverse events included in the model which are based on the adverse events that occurred in the ePAS data-set (data cut-off July 2019).

Anaemia has a cost attached of 55 635 DKK (Average of DRG codes: 16MA05 Hæmolystiske anæmier og anæmier forårsaget af enzymatiske forstyrrelser m.m.; 16MP06 Mangelanæmier). Febril neutropenia has a cost assigned of 19 268 DKK in line with current DRG. Adverse events such as neutropenia, pyrexia, weight increase and leukopenia are adverse events that are followed-up at a physician visit and do not require hospital care. The costs is 1.622 DKK (Source: Efterfølgende ambulante besøg- ONK - Rikshospital 2019 converted to 2020 according to consumer index). Patient costs for transportation and an one hour loss in income are added on (valuation of time invested in treatment (179 DKK per hour) and transportation costs per hospital visit (100 DKK per visit) (Medicin Rådet 2020).

The patient costs are based on the transportation cost of 100 DKK and an hourly loss of income of 179 DKK (Medicin Rådet (2020) Værdisætning af enhedsomkostninger). In the model we have assumed that the costs take place in the oncology visit, which is assumed to be one hour and are also included in the administrative visits when doxorubicin is given at the hospital.

Adverse events are requiring a physician visit are updated to include a patient costs of 179+100 DKK as above. Also, inpatient care costs have an eight-hour income loss included. Paediatric patients do not have a loss in income, but a parent is required to be with the child and thus have a loss of income.

No patient costs are added for advanced home care and end of life costs as DRG costs were applied. "Tilsvarende kan der også an-vendes DRG/DAGS-takster som gennemsnitsestimater for omkostninger frem for en op-splitning på delelementer."

Table 9. Adverse Events grad 3 and 4 in the model

Adverse Event	Vitrakvi® Overall (n=164) (Bayer 2020)	Vitrakvi® Adults (n=116)* (Bayer 2020)	Vitrakvi® Paediatrics (n=59)* (Bayer 2020)	Doxorubicin (Judson et al 2014)
Anaemia, %	10	10	7	4.48%
Fibril neutropenia, %	-	-	-	13.45%
Leukopenia, %	5	5	-	17.94%
Neutropenia, %	10	-	20	37.22%
Pyrexia, %	-	-	5	-
Weight increase, %	5	-	10	-
*includes patients from ePAS4 and 7 adults and 4 paediatric patients that have a follow-up time shorter than 6 months.				

6.4.4 Resource use and costs

Each health state is associated with the use of health care resources. The average long-term resource use per month has been validated by clinical experts (oncologist Jon Kindblom and Kjetil Boje). It is assumed that resource utilization is similar in the different treatment arms. This assumption will potentially overestimate the use of resources for Vitrakvi® according to validation interviews with clinical experts, as expected use is lower with a targeted treatment compared to doxorubicin. Thus, the estimate is conservative.

Drug costs are applied in the beginning of the treatment cycle.

Treatment costs

The treatment costs for Vitrakvi® and doxorubicin, respectively, are included as long as the patient does not progress. Some patients, all of whom are children, go through surgery leading to pathological complete response. These patients, 5.5% in the base case scenario, are believed to have the potential to be cured and hence no treatment costs are assigned to those patients from the transition point onwards.

Vitrakvi® is available as capsules and in oral solution to facilitate use in paediatric and adult patients. The different pack sizes have different price per mg on list-price level due to International Reference pricing. [redacted] The model assumes that the 100 mg capsule package is used. The average dosage is based on the average dosage in the Vitrakvi® trial.

Because the price differs slightly between packages, we assume that children mainly use the oral solution, while adults use the 100 mg package. In the Vitrakvi® trial, the average age of children is 2.9 years. Children will therefore mostly use the oral solution. Once paediatric patients turn into an adult at year 18 onwards the adult dosage applies.

Please note that currently only the packages with 25 mg capsules and the oral solution are available. But with regards to the price agreement with Sundhetsstyrelsen the price of the 100 mg package will be the same price per mg as the currently valid for the 25 mg capsules pack.

There are no administrative costs for Vitrakvi®.

Treatment Costs

Larotrectinib

Drug cost (DKK)	Price	units	mg/unit	Cost per mg	[redacted]	Cost per week
Adults (capsules)	44 840	28	100	16,01		21 142
Paediatrics (capsules)	44 840	28	100	16,01		14 429
Average						19 665

Patients with a long-term response an anti-tumour treatment are assumed to be stable and hence follow-up and monitoring visits are denser. This is based on the description by clinical experts. In the excel file costs are divided into the respective sheets: Treatment costs, adverse events and health state costs. Patient costs are added on for the specific unit such as physician visits and inpatient care.

Results are presented in the sheet "cost per patient" according to testing, treatment costs, adverse events and health state costs. Costs derived in the progression and progressed health state do show hospital costs as they include monitoring costs (blood samples, imaging costs, specialist costs and hospitalisation)

Since the Vitrakvi trial is a singled armed study we understand that we need to validate the relative effect versus doxorubicin (BSC) extra carefully and furthermore validate the extrapolated long-term OS.

For the validation of the relative effect versus doxorubicin we have used GMI-index as described in earlier section above.

For the validation of the long-term OS-extrapolation we have used several methods:

- Validation using Imatinib and Crizotinib long term OS-publications
- Validation using Entrectinib
- Validation of the mixture cure approach using parametric functions, AIC /BIC. The parametric model has shown to validate the mixture cure model very well both in terms of cost and effect.
- The KM OS-curve for Entrectinib lies even below Imatinib and that the KM OS curve for Vitrakvi lies highest of all these compounds: Vitrakvi has the most patients with CR and PR of all these compounds.

Testing cost in Denmark

In the NICE decision you can find the following:

> The ERG finally explores a scenario including testing costs and examines its likely impact on cost-effectiveness. The weighted overall cost of testing for larotrectinib applied in the model is £18,670. In this scenario, the cost of testing was added as a one-off cost to the total costs of larotrectinib. The ICER for larotrectinib, including this testing cost is [redacted] per QALY gained when assuming a 64% ORR (ePAS2 population estimated from the BHM), and [redacted] per QALY gained, when assuming a 57% ORR (full integrated efficacy analysis population estimated from the BHM).

So the NICE-decision itself does not help in elaborating around the testing cost of £18 670. However, this is a “ball park figure” to use for validation when we estimate the testing cost from a Danish and Scandinavian

perspective interviewing oncologists, pathologists and payers in the different countries. Below is how we have resonated and estimated the testing cost from a Danish perspective:

Tests that are part of routine medical care as a non-targeted diagnostic (eg at the time of diagnosis, 'diagnostic tests') should not normally burden the health economy of the individual drug, while tests that are performed and required to identify the target for a specific treatment may burden the drug in question, so called 'directed tests'.

However, with the event of precision medicine, many countries are now implementing 'broad genetic testing' with whole genome sequencing (WGS) or next generation sequencing (NGS), which detects multiple genes, e.g. cancer-specific NGS-panels that detects 500+ genes. This is more cost- and tissue- effective, in part, this has to do with how testing has been done: sequential single-gene tests such as PCR or FISH, with each test using up valuable tissue and time, and each test has a cost, and leads to tissue exhaustion, where any subsequent test has a significantly lower rate of success.

A much more elegant solution is a multiplexed assay that can examine all the targets of interest at once - but how does it compare to single gene tests on cost? In other words, would it cost more to do multiple tests, each individually less expensive than NGS, than to do a single test for all required markers but that costs more? And how does this affect turnaround time and success rates?

Studies have looked at the cost and turnaround time of NGS to multiple simultaneous and sequential SGT strategies (Pennell et al 2018 & 2020, Steuten et al 2019). The results indicated that for the four current recommended markers in NSCLC, NGS testing was both less costly and faster than any strategy that used single-gene tests, and perhaps most importantly, it identified the highest percentage of patients with targetable findings. This imbalance will only become more marked as we move to use an increasing number of gene alterations - indicating that this is a dynamic process, and that the costs will decrease with time.

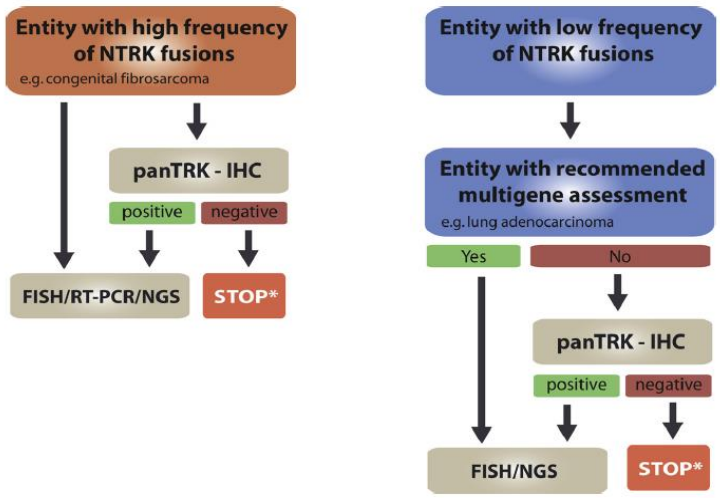
The goal of the introduction of precision medicine is thus to avoid directed tests; instead, the goal is for treatments and follow-ups to be based on broad genetic testing, depending on positive or negative read-outs. In Sweden, Genomic Medicine Sweden (GMS; https://genomicmedicine.se/en/) expects to implement cancer-specific NGS-panels containg about 560 genes, and GMS expect to reach 50 000 broad NGS-sequencing tests within five years, an increase of about 10 000 test per year (about 10 000 tests 2021). If we assume the same process in Denmark it will translate into 25 000 broad tests within five years, an increase of about 5 000 tests per year.

In regards to NTRK-fusion testing, we have suppled 2 different calculations to the Swedish HTA agency TLV:

Testing of NTRK-fusions for diagnostic purposes is currently limited to high frequency malignancies, infantile fibrosarcoma, secretory carcinoma of salivary gland, secretory breast cancer, and congenital nephroma; detection of NTRK fusion is part of the diagnostic process to reach the correct diagnosis and is not done (today) for treatment predictive purposes. In these cases, the variant ETV6-NTRK3 is usually examined with RT-PCR or FISH (usually FISH ETV6).

Treatment predictive testing is governed by the needs of oncology, which in turn is mainly governed by guidelines. However, today most solid tumour guidelines have not yet included NTRK fusion testing, but different proposals have been put forward (Figure 1):

Figure-1: Proposed NTRK-fusion testing algoritm (Märkl et al, Pathology Research and Practice 2019;215:10:152572).



**Despite its high sensitivity, negative IHC does not rule out a NTRK fusion in 100% of cases. (Märkl et al, Pathology Research and Practice 2019;215:10:152572)*

However, as there currently are no established pan-tumour algorithms, and since testing and treatment may differ between tumour indications and treatment-lines, we have made two different conservative estimates on how many may be tested yearly in Denmark:

1) Directed testing:

In Denmark, approximately 30 000 patients were diagnosed with a cancer type during 2018. NTRK-fusions are extremely rare and only isolated cases have been seen in for example prostate cancer (ca 5 500 patients per year) or breast cancer (with ca 5 000 new patients per year) or blood and lymph tumours (ca 4 500 new patients per year). Since only isolated cases has been seen in these cancer types above, they are excluded from our calculation. Instead we concentrate on high frequency of NTRK fusions that today already are detected via diagnostic testing. We also concentrate on low frequency of NTRK fusions that are already being tested with multiplex or NGS testing; such as non-small cell lung cancer (NSCLC), malignant melanoma, and in some regions also colon cancer, as broad testing is unevenly introduced today.

We then have 17 500 patients left in Denmark. We have taken these figures from the National Board of Health and Welfare's cancer register. The recurrence rate of tumour diseases where NTRK fusions occur varies; glioblastoma almost 100%, soft tissue sarcoma 50%, renal cancer 13%, thyroid 30%, pancreas 36%, NSCLC 26%, osteosarcoma 11-12%.

If we count conservatively, this means that about 50% of these 17 500 patients, i.e. 8 750 patients develop a locally advanced or metastatic disease, which is the indication area for Vitrakvi (excluding the small group of mainly children where mutilating surgery is the alternative to treatment). In the calculation based on epi-data, we have assumed that 50 NTRK fusion-positive patients can potentially be found per year in Denmark. The cost of IHC screening of these 8 750 patients will be DKK 4 812 500 if an IHC test costs DKK 550 DKK.

However, IHC tests that measure the presence of protein have a margin of error so we get more false positive patients (Rudzinski et al 2018, Hechtman et al 2017), than true positive patients. With a population of 8 750,

we can count on about 450 false positives and 100 true positives, i.e. around 550 patients need to be validated with NGS. Since it is a verification, no broad panel is needed, hence a smaller commercial NGS panel can be used, with a test of about DKK 3 600. We have used an average amount of DKK 5 000 for this verification analysis. The prices for both IHC and NGS have been communicated to us by pathologists in active clinical practice and the prices seem to vary between different hospitals.

If we add up, the cost per validated NTRK fusion patient will be DKK 151 250:

IHC: 8 750 patients x 550 DKK = 4 812 500 DKK

NGS: 550 patients x DKK 5 000 / analysis = 2 750 000 DKK

Patient cost: (DKK 4 812 500 + DKK 2 750 000) / 50 = DKK 151 250 per identified patient

2) Broad testing (NGS):

A goal for Genomic Medicine Sweden (GMS) is to develop and implement in clinical routine multiplex NGS panels for adult tumours for simultaneous identification of changes in 560 genes relevant to the development of cancer and for choice of treatment, and to establish nationally uniform analysis tools for equivalent diagnosis and treatment in the entire country.

Already today, about 5 000 NGS analyzes are performed in total in Denmark (all diagnoses, including cancer) with commercial NGS panels (15-50 genes); in dialogue with GMS it appears that they aim to within about five years to perform about 50 000 tests on cancer patients samples in Sweden for the treatment and follow-up, based on broad genetic analysis, either whole genome sequencing (children) or GMS-developed and validated cancer panels (NGS cancer panels with 560 cancer genes). If we assume the same pathway for Denmark it will be about 25 000 tests in Denmark.

A wide NGS panel with 560 genes costs about 8 700 DKK in Denmark. If the cost of introducing these NGS tests is to be charged to Vitrakvi, we can expect the NTRK fusion part of the test to be 1/560 part, and the costs per year will be as follows:

Year	Estimated number of tested patients/year		DKK/panel		fraction per gen of totally 560 genes		% of the cost in the Vitrakvi-arm		Total yearly cost, DKK	DKK/pat	Average cost per patient and year during 45 years
1:	5 000	*	8 700	*	1/560	*	100	=	77 679	15.5	
2:	10 000	*	8 700	*	1/560	*	100	=	155 357	15.5	
3:	15 000	*	8 700	*	1/560	*	75	=	174 777	11.7	
4:	20 000	*	8 700	*	1/560	*	50	=	155 357	7.8	**1.2 DKK**
5:	25 000	*	8 700	*	1/560	*	25	=	97 098	3.9	
6:										0	

In the calculation above, we charge Vitrakvi 100% in years one and two, with a depreciation of 75%, 50% and 25% in years 3-5. We then calculate the average cost per patient and year it will be under 45 years to be able to easily apply this to the model with a price increase for Vitrakvi. If we do, the cost per patient and year will be 1.2 DKK. This for the following reasons:

1) Broad NGS tests is a cost-effective and patient-friendly way for society to handle testing, and to implement precision medicine, finding the right patient and avoiding unnecessary delay and costs.

2) Implementation of broad multiplex testing means that testing will gradually increase in both arms of the cost model. Gradually, the cost of broad genome sequencing will become a practice, and then it will be used in both arms of the calculation, i.e. also in the proxy control arm BSC or doxorubicin arm.

Treatment costs for comparator

For comparator treatments, drug acquisition costs of generic compounds are sourced from medicinpriser.dk. The least expe1.622nsive cost per mg of drug is used to represent unit cost, and drug wastage is not considered for comparators in the base case. To estimate average doses and expected cost of doxorubicin, dose recommendation in Judson et al (2014) (75 mg/m²) is combined with BSA in the Vitrakvi® clinical programme (adults: 1.88 m^2, paediatric s: 0.74 m^2).

Table 12: Treatment drug cost for comparators included in the model

Treatment	Dosing schedule	Dose per treatment cycle, mg	mg per pack	Expected pack cost (DKK, PPP)	Expected cost per day (DKK, PSP)	Source
Doxorubicin	Average dose of 75mg/m2 BSA once per 21-day cycle for 6 cycles	141	200	360	10	Medicinpriser.dk (Adriamycin 100 ml solution (2mg/ml)) BSA from adults in larotrectinib clinical trial program

The doxorubicin treatment entails one 72-hour continuous intravenous infusion every 3 weeks and last until progression for up to six cycles (Judson et al 2014).

Administration cost for doxorubicin is based on the administration procedure(s) required in each treatment cycle and the number of administrations. The administration of doxorubicin is described as either 75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion (Judson et al 2014). As the patients considered for Vitrakvi® both in the clinical programme and in clinical practice will have progressed on several previous therapies and are either locally advanced or metastatic, it is assumed these patients are frail and would require a longer, more gentle chemotherapy administration. An administration cost reflecting DRG code for administration of chemotherapy (table 13).

The administration cost in part also reflects a cost carried by parents of the fraction of paediatric patients, having to accompany the child through chemotherapy treatment.

Table 13. Doxorubicin administration costs

Administration type	Code	Unit cost (DKK)
Deliver simple parenteral chemotherapy	Average DRG takster 2020 of 27MP17-27MP24	27 242

Treatment with doxorubicin is assumed to take place on a full day (8h) in the hospital. Therefore, patient costs (indirect costs) occur according to MR handbook being the following costs: valuation of time invested in treatment (179 DKK per hour) and transportation costs per hospital visit (100 DKK per visit) (Medicin Rådet 2020). The costs are included as a one-off cost being 1532 DKK (8*179+100) and added for each cure of chemotherapy.

Resource use and health care costs

We have used sarcoma as a basis for resource frequencies in our models, and have used the Danish and Swedish guidelines for sarcoma (Klinisk Retningslinje kræft, DSG –Dansk Sarkom Gruppe (Version 1.2, Faglig godkendelse 09. januar 2019 (DSG), and Skeletal and soft tissue sarcoma in extremities and trunk wall, Swedish National Care Program, 2020, Version: 2.0) and Swedish guidelines for palliative care (National care program for palliative care in the end of life, revised in 2016).

The palliative care program describes palliative care in the final stages of life, regardless of diagnosis, age, ethnicity, background or other factors. After completion of anti-tumor treatment, the follow-up routines are very different between clinics. Clinical examination of the surgical area and examination of the lungs (lung X-ray or CT of the thorax) are most important. MRI / CT of the surgical area is performed less frequently, but most often at signs of recurrence.

Blood tests do not usually reveal any recurrence. How often checks are performed depends on the risk of recurrence, in the case of low-grade sarcomas, a common model is a check-up every 6 months for 3 years and then annually for at least 5 years. In high-grade sarcomas (grade 2-3), check-ups are common every 3 to 4 months for the first 2 years, followed every six months to 5 years and finally annually for at least 5 years. On average, the frequencies are given for progression-free and progressed. A minimum palliative team can consist of district physician, district nurse, and home care staff, as needed supplemented with paramedical expertise in the hometown.

Monitoring costs during and after progression as well as costs for chemotherapy are included in the model. Resource utilization per treatment cycle is the same regardless of treatment arm. As time spent in each health state differs for the respective treatment arm the total costs will differ between the arms.

Bayer consulted two clinical experts on the resource use when treated with either treatment options. Physicians outlined that they do not find that, for example, follow-up visits differ between the treatment alternatives in the progression and progressed health state. However, as outlined in the application, the clinical experts described that patients with a long-term response require less follow-up visits/monitoring of the disease over time. The experts estimated that from year 3 onwards, the follow-up visits and monitoring of the disease is on average 2.4 times a year rather than every month. As long-term responders can only be found in the Vitrakvi® arm, one can say that a difference between treatment alternatives has been shown. This is however based on the effect of the respective treatment.

Each physician visit has an indirect cost attached to it of 279 DKK (=1h for a physician visit and 100DKK per transportation cost).

Resource utilization for the progression-free stage is an average per treatment cycle for the entire lifetime horizon. During the first three years, monitoring events are significantly denser in the progression-free stage and then decline. As a conservative approached, we assume that follow-ups only become sparse after three years with a medical check up to once every six months, even though one can argue that it visits for patients with a long-term response would already be denser after two years.

Patients with both locally advanced and metastatic tumours are commonly treated with surgery for palliative reasons. Surgery is undertaken to ease the disease burden by minimizing the tumour size. The tumour can lead to pressure on other organs when located internally, but also be a motorial burden for the patient when located externally. The cost of surgery is excluded, as all patients are assumed to experience surgical intervention at some point. Whether it happened early or late in the course of disease was considered

irrelevant. However, surgery in the progressed patients is considered an additional intervention in the current HTA.

For some histological subtypes with TRK fusion cancer, especially soft tissue sarcom cancer (STS) and infantile fibrosarcoma (IFS), mutilating surgery is the only alternative. The consequence is functional loss of a limb in order to reach curative status, even with currently available neoadjuvant chemotherapy options (Orbach 2016). Vitrakvi® showed that for patients where no other curative options besides amputation or disfiguring surgery was available, amputation has been avoided with Vitrakvi® treatment.

Costs for the end of life are based on a total one-off cost. A detailed description and unit costs are found in Appendix 1.

6.5 Subgroup analysis for paediatric patients with TRK-fusion cancer

The efficacy for paediatric patients being treatment with Vitrakvi® is exceptional from the overall population:

- ORR is 95-100% for paediatric patients compared to 79-80% for the overall population for ePAS-data and PAS respectively.
- In the PAS-data the probability for survival at 12-month is 100% for paediatric patients compared to 90% for the overall population.
- In the ePAS-data the probability for survival at 12-month is 98% for paediatric patients compared to 90% for the overall population.

The long-term cost for treatment with Vitrakvi® in paediatric patients is compared to doxorubicin and the Proxy-control arm BSC. As almost all paediatric patients respond to treatment with Vitrakvi® the non-responder group for paediatric patients is too small to create their own Proxy-control arm BSC. Hence, Bayer use the Proxy-control arm BSC for the entire patient population as a comparison arm in the cost analysis among paediatric patients. As shown in section 6.4. showing the intra-patient comparison for paediatric patients is justified.

RRs for PFS and OS for patients in the long-term survivor group among paediatric patients is constant relative to the general population.

The effect of the analysis for children, just as for the entire patient population, is taken from PAS data, which includes 12 children with continuous follow-up. The table below summarizes the effectiveness in paediatric patients with TRK fusion cancer.

Table 14. Vitrakvi® efficacy in paediatric patients with TRK-fusion cancer (PAS and ePAS-data)

	[redacted]
Total paediatric patients	
Age, mean (years)	
ORR, n (%)	
CR	
PR	
CR+PR with DoR ≥24 months	
Pathological complete responders, n (%)	
Data cut-off: july 2019	

[redacted]. 25% (3 of 12) have received pathological complete response after successful surgery, after which they have been able to terminate treatment with Vitrakvi® without recovering their cancer. Further follow-up studies will show whether the possibility of a potential cure remains. The proportion of long-term survivors in the long-term survivors group among paediatric patients in PAS-data is thus a total of 58.3% (7 of 12). Figures 29 and 30 below show the OS for children in PAS-data and ePAS-data with a clear plateau phase.

Figure 29. OS for paediatric patient in the Vitrakvi®-trial (PAS-data)

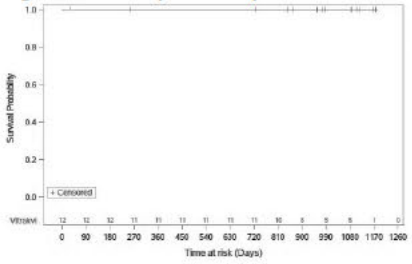
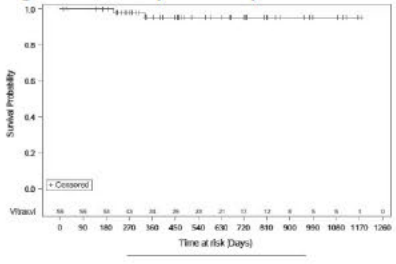


Figure 30. OS for paediatric patient in the Vitrakvi®-trial (ePAS-data)



Data cut-off July 2019

7 Results - The overall patient population with TRK-fusion cancer

7.1 Mixture cure model: base case overall population

[redacted]

Larotrectinib: Overall patient population

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Larotrectinib	[redacted]						
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							
Death							

Progression free

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Larotrectinib	[redacted]						
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							

Progressed

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Larotrectinib	[redacted]						
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							

Doxorubicin

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Treatment							
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							
Death							

Progression free

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Treatment							
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							

Progressed

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Treatment							
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							

Difference Larotrectinib vs. Doxorubicin (Total)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)	Lifetime (discounted)
Treatment							
Other drugs							
Healthcare							
Monitoring							
Testing							
Adverse events							
Patient transport							
Patient loss of income							
Death							

7.2 Sensitivity analysis with parametric model

In the below analysis we have used the parametric curve with lowest AIC/BIC, log normal function, for long term OS-extrapolation. This scenario validates very well the base case scenario in the mixture cure model. [redacted] The model is adapted specifically for the Danish setting to calculate the costs for years 1-5 in addition to an 80-year life-time horizon. The results are presented per patient and can consequently be multiplied to obtain an estimated result for a given number of patients.

The Markov trace from the original model is used and consequently the patient distribution matches the original cohort model. The only difference in health state distribution is that the model includes Danish background mortality from 2017-2018 and therefore matches the Danish setting.

Patient life-years are calculated but not part of the result while the quality adjusted life-years have been disabled. Costs are discounted with 4 % for years 1-34 and 3% for year 35 and beyond.

Unit prices, resource use and discount rates can be controlled from the 'Costs per cycle' sheet. The unit for resource use is per cycle which corresponds to resource use per patient and week.

Model, parametric and Larotrectinib settings can be controlled from the 'Settings' sheet where the proportion of adults, children, men, and women can be adjusted. Additionally, the age of adults and children as well as treatment duration can be changed.

7.1 Subgroup analysis for the paediatric population in the mixture cure model

The model estimates the total discounted average difference in cost between Vitrakvi and Doxorubicin is [redacted] during the first 5 years.

	Difference Total year 1 to 5 Vitrakvi versus Doxorubicin									
Year	Treatment	Other drug	Heathcare	Monitoring	Testing	Adverse	Transport	Loss of	Death	Total
1st year	[redacted]									
2nd year										
3rd year										
4th year										
5th year										
	Difference Total lifetime Vitrakvi versus Doxorubicin									
Life-Time	[redacted]									
Undiscounted										
Discounted										

8 Conclusion of the cost analysis

The incremental cost per patient for Vitrakvi® versus Doxorubicin is [redacted] during the first 5 years and [redacted] for a lifetime perspective for the overall population

[redacted]

A subgroup analysis for adults would only show similar or probably lower costs than they are accounted for in the base case meaning the overall population. This is based on the known fact that paediatric patients have the greatest long-term survival when assuming a life-time horizon of 80 years as is the case in the base-case scenario.

A driving factor in the model is the proportion of patients with pathological complete response. These patients may have the potential for potential cure, for how long follow-up studies may show. In the Vitrakvi® trial some patients are listed as having no other curative options besides amputation or disfiguring surgery. Following treatment with Vitrakvi® surgical treatment has become an option, but with no disfiguring consequences. Patients undergoing these surgeries can reach pathological Complete Response and thus discontinue treatment with Vitrakvi®.

Also, the time horizon is a driving factor. [redacted]

Assumptions that underly the effect of Vitrakvi® over time have been validated against historical cohorts with imatinib and Xalkori® as well as with clinical experts[redacted]

We believe that treatment with Vitrakvi® meets the criteria stipulated in the Act on Medicine Council certainly with regard to the severity and rarity of TRK fusion cancer.

Wastage is not included in the model as the dose can be adjusted with the available formulas. For example, paediatric patients differ in weight certainly as patients from all age groups are included and hence the oral solution can be adjusted accordingly. However, the Dosage (mg/day) can be changed.

9 Budget Impact: base case overall patient population

TRK fusion cancer is considered a rare disease, with an estimated prevalence that is below the threshold criteria for an orphan disease (the threshold is defined as a disease state affecting not more than 5 in 10 000 people in the EU and 1-2 in 10 000 people in Denmark) (Commission of the European Communities 2008 and Rigshospitalet 2015). The incidence is estimated to 1.04 per 100 000 citizens in Denmark. For legal reasons, EMA was not able to combine the orphan drug status with the tumour diagnostic indication.

Although rare, these pan-cancer kinase fusion events are known to drive tumourigenesis across the multitude of histologies in which they are present (Stransky 2014, Lange 2018).

The majority of the data on the frequency of *NTRK* gene fusions is based on the specific tumour histologies included in the Vitrakvi® trial. In ePAS data (July 2019) 21 solid tumour histologies are included to date.

Bayer has run a systematic literature review which summarizes data on the frequency of *NTRK* gene fusion in solid tumours in order to determine the incidence in Europe.

To estimate the incidence of TRK fusion cancer the general frequency of specific tumour types in the overall population is first established. Thereafter the tumour occurrence is combined with the frequency of NTRK gene fusion. Tumour types not reported in the literature are assumed to have an *NTRK* gene fusion frequency of 0%. As this is still a developing field, the interpretation of the *NTRK* gene fusion incidence should be considered carefully.

Based on the knowledge, that there are 4 602 445 adult people living in Denmark (Statistics Denmark 2020), we estimate that there are 48 adult patients that have TRK fusion cancer.

For adults, we assume that today's testing frequency is 10% the first year and increases by 10% annually. This means that the number of patients with diagnosed TRK fusion cancer who can be treated with Vitrakvi® are 5 patients the first year, see Table 22. As outlined testing patterns are moving to whole genome sequencing which will improve the diagnostic of TRK fusion cancer and might hence change.

Table 22. Overview on adult patients with TRK fusion cancer based on testing frequency

Year	Patients annually	TRK fusion cancer diagnosis	Patients diagnosed annually	Market shares	Uptake
2020	48	10%	5	[redacted]	
2021	48	20%	10		
2022	48	30%	14		
2023	48	40%	19		
2024	48	50%	24		

The budget impact calculation is based on the same costs as valid in the cost-analysis. Patients not treated with Vitrakvi® are assumed to receive doxorubicin.

The average cost per adult patient over the first five years in shown in the Table 23 and Table 24.

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11 Appendix

11.1 Appendix 1. Resource use and unit costs

Resource utilization for the progression-free stage is an average per treatment cycle for the entire lifetime horizon.

Two clinical experts stated that the first three years of monitoring are significantly more dense in the progression-free stage and then decline. For this reason, resource utilization in the progression-free stage is based on an average of 40 years, with the first three years adopting closer monitoring of the patient than the remaining years.

Resource use	Progressionfree the first 3 years in the cost-analys (per month)	Progressionfree the remaining 37 years in the cost-analys (per month)	Progressed disease (per month)
CT-scan	0.5	0.2	0.2
Bloodtest	1	0.2	0.3
Liverfunctiontest	1	0.2	0.3
Ondansetron 4mg	6	0	0.5
Paracetamol 500mg	24	0	1.8
Oxynorm 10mg	9	0	0.7
Dexamethasone 2mg	6	0	0.05
Afipran 10mg	6	0	0.5
Ambulant care	1	0.2	0.3
Inpatient care	0.2	0	0
Palliative Care	0.2	0	0

Component	Progressionfree	Progressed disease	Unit cost (DKK)	Unit cost source
Outpatient/inpatient visits				
Oncology visit	0.3	3	1 622	Efterfølgende ambulante besøg- ONK - Rikshospital 2019 converted to 2020 according to cosumperindex.
Inpatient care	0	1	30 432	Indlæggelse grundet leverkræft, DRG 30 167 Ondartet sygdomme i lever, galeveje og bugspytkirtel, pat. mindst 18 år. converted to 2020 according to cosumperindex.
Advanced home care	0	1	6251	Specialiseret Palliativ indsats, Lille, Hjemmebesøg DRG takster 2020 26HJ03
Diagnostic tests				
CT-scan	0.2	0.5	2032	30PR06; CT-scanning, komplicerat - DRG takster 2020
Full blood count	0.3	1	-	Included in ambulant care
Liver function test	0.3	1	60	ASAT+ ALAT–Rigshospitalets metodeliste 2020 https://labportal.rh.dk/Metodeliste.asp?Pris=Show
Pain management				
Ondansetron 4mg tabs	0.5	12	0.86	Ondansetron "Bluefish" - medicinpriser.dk
Paracetamol 500mg tabs	1.8	48	0.43	Arax - medicinpriser.dk
Oxynorm 10mg tabs	0.7	18	3.90	OxyNorm Dispersa - medicinpriser.dk
Dexamethasone 2mg tabs	0.5	12	1.58	Dexamethasone "Krka" (4mg devided by 2) - medicinpriser.dk
Afipran 10mg tabs	0.5	12	0.33	Metoclopramid
End of life care				
Palliative resection	0	0.05	96472	Større operationer ved øvrige svulster, pat. 0-17 år 26MP27 DRG takster 2020 Note: This is the most relevant cost to represent palliative resection even tough there is an age discrepancy.
Terminal care hospice/palliative unit			88801	Specialiseret Palliativ indsats, Stor, 26MP45 DRG takster 2020

Medicinrådet

Medicinrådets protokol for vurdering af larotrectinib til behandling af NTRK-fusion-positiv kræft

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om protokollen

Protokollen er grundlaget for Medicinrådets vurdering af et nyt lægemiddel. Den indeholder et eller flere kliniske spørgsmål, som ansøger skal besvare i den endelige ansøgning, og som Medicinrådet skal basere sin vurdering på.

Lægemidlet vurderes efter Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser – version 2. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	19. februar 2020
Ikrafttrædelsesdato	19. februar 2020
Dokumentnummer	72688
Versionsnummer	1.0

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 19. februar 2020

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Vitrakvi
Generisk navn	Larotrectinib
Firma	Bayer A/S
ATC-kode	L01XE53
Virkningsmekanisme	Larotrectinib er en tropomyosinreceptorkinase (Trk)-hæmmer, som hindrer neurotrophin-Trk-interaktion og dermed Trk-aktivering. Dette inducerer celledød og hæmning af celledeling i tumorer, som overudtrykker Trk.
Administration/dosis	Kapsel 100 mg to gange dagligt (voksne) eller 100 mg/m^2 to gange dagligt (børn). Se afsnit 4.2.
EMA-indikation	"Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have no satisfactory treatment options". Godkendelsen er betinget ('conditional approval').

2 Forkortelser

AE:	Uønsket hændelse *(adverse event)*
ARR:	Absolut risikoreduktion
BSC:	*Best supportive care*
CHMP:	*Committee for Medicinal Products for Human Use*
CI:	Konfidensinterval
CR:	*Complete response*
CTCAE:	*Common Terminology Criteria for Adverse Events*
EMA:	Det Europæiske Lægemiddelagentur *(European Medicines Agency)*
EORTC QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European public assessment report*
ESMO:	*European Society for Medical Oncology*
FISH:	*Flourescence in situ hydridization*
GRADE:	System til vurdering af evidens *(Grading of Recommendations Assessment, Development and Evaluation)*
HR:	*Hazard ratio*
IHC:	*Immunohistochemistry*
ITT:	*Intention-to-treat*
MCBS:	*Magnitude of Clinical Benefit Scale*
MKRF:	Mindste klinisk relevante forskel
NGS:	*Next Generation Sequencing*
OR:	Odds ratio (*odds ratio*)
ORR:	*Objective response rate* (objektiv responsrate)
OS:	Overlevelse (*overall survival)*
pCR:	patologisk komplet respons
PFS:	Progressionsfri overlevelse (*progression-free survival)*
PR	*Partiel respons*
R0:	komplet resektion
RR:	Relativ risiko
RECIST:	*Response Evaluation Criteria in Solid Tumors*

3 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af larotrectinib som mulig standardbehandling af patienter med lokalt avancerede eller metastaserende solide tumorer, som uanset tumortype har fået påvist en genfusion af neurotrofisk tyrosinreceptorkinase (NTRK), og som ikke har andre acceptable behandlingsmuligheder. I protokollen angives en definition af population(er), komparator(er) og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende larotrectinib modtaget den 22. november 2019.

Protokollen danner grundlag for den endelige ansøgning for vurdering af larotrectinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem larotrectinib og placebo eller *best supportive care* (BSC) af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

4 Baggrund

En solid tumor er en unormal vævsmasse (svulst), som normalt ikke indeholder cyster eller flydende materiale. Faste tumorer kan være benigne (ikke kræft) eller maligne (kræft), hvor sidstnævnte per definition evner at gennemtrænge eller sprede sig til andre dele af kroppen. Kræft inddeles i forskellige typer, afhængig af hvilken celletype kræften udgår fra. Solidt voksende kræfttyper kan overordnet underinddeles i sarkomer (bløddels- og knoglekræft), karcinomer (epitel deriverede kræftformer), melanomer (modermærkekræft) og lymfomer (lymfekræft). Leukæmier (blodkræft) danner generelt ikke solide tumorer. For hver af disse overordnede typer af kræft findes yderligere talrige undertyper, baseret på hvilket organ eller væv de udgår fra, og hvilke histopatologiske og eventuelle molekylærbiologiske forandringer der kendetegner kræften. De forskellige kræftformer rammer forskelligt i befolknings- og aldersgrupper og kræver forskellige former for diagnostik og behandling.

Forekomsten af kræft er stigende, og ca. 1/3 af alle danskere vil få kræft i løbet af deres liv. Antallet af nye tilfælde pr. år er ca. 40.000 med en lille overvægt af mænd. Den ældre del af befolkningen står for den største andel af nye kræfttilfælde, således står mænd og kvinder over 60 år for mere end 2/3 af alle nye kræfttilfælde. Lidt over 280.000 nulevende danskere har på et tidspunkt fået konstateret kræft, og 6 ud af 10 kræftpatienter overlever deres sygdom i mindst 5 år [1].

Kræft er sjældent hos børn (under 15 år), men det er den næsthyppigste dødsårsag efter 1-årsalderen. Mindre end 1 % af alle kræfttilfælde forekommer hos børn, og ca. 170 børn får årligt konstateret kræft. Den 5-årige overlevelsesrate for børn med kræft er på ca. 80 %. Fordelingen af kræfttyperne hos børn er helt anderledes end hos voksne [1]. Voksne får således typisk karcinomer, mens børn hyppigst får blodkræft [2].

Neurotrofisk tyrosinkinase (NTRK) er navnet på en gruppe af tre gener, der koder for tyrosinreceptorkinaser (Trk) A, B og C. Trk er afgørende for normale nervecellers udvikling og overlevelse. Genfusioner, der involverer NTRK1, NTRK2 eller NTRK3, medfører ukontrolleret Trk-signalering og dermed tumorvækst [3,4]. NTRK-genfusioner er sjældne og påvises med yderst varierende hyppighed på tværs af tumortyper hos både børn og voksne. Herudover er det uvist, om der er geografiske og epidemiologiske forskelle i forekomst af NTRK-genfusioner. I enkelte sjældne kræfttyper såsom infantil fibrosarkom og sekretorisk karcinom i både spytkirtel og bryst påvises NTRK-genfusioner med en frekvens på næsten 100 %. I andre mere hyppige kræfttyper i luftveje, fordøjelseskanal, bryst, modermærker og hjerne påvises NTRK-genfusioner med en frekvens på mindre end 5 % [5,6]. For flere af de allerhyppigste kræftformer, herunder lungekræft, tyk- og

endetarmskræft, modermærkekræft og brystkræft, vurderes frekvensen af NTRK-genfusioner dog til at være mellem 0,1-1 % [7].

4.1 Nuværende og fremtidige behandling

Hovedparten af patienter med kræft modtager standardbehandling, som primært afhænger af kræfttype samt stadie, hvor operation med henblik på helbredelse oftest er førstevalg. Når kirurgisk behandling ikke er mulig eller ikke er tilstrækkelig, tilbydes patienterne enten strålebehandling og/eller medicinsk behandling (kemoterapi, targeteret behandling eller immunterapi). Den valgte medicinske behandling afhænger af mange faktorer, herunder hvilken kræfttype, hvor udbredt sygdommen er, samt om kræfttypen eventuelt udtrykker særlige molekylærgenetiske forandringer, hvortil der er udviklet specifikke (targeterede) lægemidler. Herudover skal patienterne være i tilstrækkelig almen tilstand til at kun tåle yderligere behandling. I studier måles almen tilstand ofte med ECOG-performance status [8].

For en lille andel af patienterne med meget sjældne kræftformer findes der ingen etableret standardbehandling. Derudover er der patienter med hyppigere kræftformer, som i løbet af deres behandlingsforløb udtømmer alle standardbehandlingsmuligheder. Disse patienter kan indgå i forsøg med eksperimentel behandling eller få tilbudt lindrende behandling, fremover benævnt 'best supportive care' (BSC).

I modsætning til den traditionelle fremgangsmåde for kræftbehandling, kendetegnet ved i vid udstrækning at være histologi (vævstype)-afhængig, er larotrectinib (se afsnit 4.2) ikke indiceret til én bestemt kræfttype, men til alle tilfælde af solide tumorer med NTRK-fusion (ofte benævnt som 'vævs-/tumor-agnostisk'). Af denne årsag, og fordi larotrectinib er indiceret, når øvrige acceptable muligheder for behandling er udtømte, findes der ikke standardbehandling for de patienter, som kandiderer til behandling med larotrectinib. Derfor kan der heller ikke fastslås et enkelt eller nogle få medicinske behandlingsalternativer til larotrectinib.

4.2 Larotrectinib

Larotrectinib hæmmer tropomyosinreceptorkinaserne (Trks), som er kodet af generne NTRK1, NTRK2 og NTRK3 [6,9,10]. Fusioner af disse gener med forskellige andre gener kan resultere i aktiverede kimære trk-fusionsproteiner, som kan virke som 'onkogene drivere' til fremme af celledeling og overlevelse af tumorceller.

Patienter kan behandles med larotrectinib, hvis de har en NTRK-genfusion i en tumorprøve. Der testes ikke rutinemæssigt for NTRK-genfusion i tumorprøver, og der er ingen klinisk validerede tests eller 'companion diagnostics' tilgængelige til at udføre testen. Man kan både anvende *next-generation sequencing* (NGS), immunhistokemi (IHC) og *flourescence in situ hydridization* (FISH) for at påvise fusioner (se afsnittet 'andre overvejelser').

De anbefalede doser af larotrectinib for voksne og børn med et kropsareal ≥ 1,0 m^2 er 100 mg oralt to gange dagligt. Til børn med et kropsareal <1,0 m^2: 100 mg/m^2 oralt to gange dagligt (maksimalt 100 mg pr. dosis). Behandlingen fortsættes indtil sygdomsprogression eller uacceptabel toksicitet. Startdosis bør reduceres med 50 % hos patienter med moderat eller svær nedsat leverfunktion. Der kan ved forekomst af bivirkninger foretages op til tre dosisreduktioner af 25 mg pr. reduktion (se tabel 1 i produktresumé).

Antallet af patienter, der årligt er kandidater til behandling med larotrectinib i Danmark, er usikkert. Dels findes der ikke tilstrækkelige data for hyppigheden af NTRK-fusion hos danske kræftpatienter, og derudover er larotrectinib først indiceret, når alle øvrige acceptable muligheder for behandling er udtømte. Derfor skal

et estimat af patientantal tage højde for frafald imellem behandlingslinjer på tværs af mange forskellige kræftformer.

En af forudsætningerne for behandling med larotrectinib er, at alle øvrige behandlingsmuligheder er udtømte. I denne sammenhæng henviser fagudvalget til gældende nationale retningslinjer og Medicinrådets behandlingsvejledninger indenfor de forskellige relevante kræftområder.

Fagudvalget skønner, at der årligt er ca. 10.000 danske patienter, som har uhelbredelig kræft [2], og at ca. 1/3 af disse vil udtømme alle acceptable behandlingsmuligheder men stadig være i tilstrækkelig performancestatus til at modtage yderligere behandling. Dette er baseret på et skøn af det typiske antal behandlingslinjer og frafald herimellem. Det er således i denne population af ca. 3.300 kræftpatienter, at man skal identificere de patienter, som kan være kandidater til behandling med larotrectinib.

Fagudvalget tager i sit skøn højde for, at der vil være ganske få patienter med meget sjældne kræftformer, hvor NTRK-genfusionen er hyppig (f.eks. infantil fibrosarkom) samt mange patienter med hyppigere kræfttyper (f.eks. tyk- og endetarmskræft, lungekræft og modermærkekræft), hvoraf kun ganske få (ca. 0,3 %) vil have en NTRK-fusion. Derudover skønner fagudvalget, at der blandt de 1.400 årlige tilfælde af hjernetumorer i Danmark [2] vil være ca. 10 patienter, som kan have gavn af behandlingen. Fagudvalget skønner således samlet, at mellem 10 og 40 patienter årligt kan blive kandidater til behandlingen i Danmark.

Fagudvalget understreger, at der ikke foreligger tilstrækkelige data til at foretage en valid vurdering af antallet af patienter, hvorfor ovenstående skøn er forbundet med væsentlig usikkerhed. Estimatet afhænger tilmed i vid udstrækning af, hvordan screening efter NTRK-fusion implementeres.

Fase-1-enheden på Rigshospitalet deltager i den kliniske afprøvning af larotrectinib. Fagudvalget oplyser, at der siden forsøgsstart i 2016 kun er inkluderet én dansk patient.

Fagudvalget bemærker, at ansøger i den foreløbige ansøgning har estimeret, at ca. 30 patienter årligt kandiderer til behandling med larotrectinib i Danmark. Dette estimat er heller ikke baseret på konkrete data.

5 Kliniske spørgsmål

De kliniske spørgsmål indeholder en specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål. De kliniske spørgsmål er udformet, så der skelnes mellem voksne og børn.

Larotrectinib er ikke indiceret til én bestemt kræfttype men til alle tilfælde af solide tumorer med NTRK-fusion, når øvrige acceptable muligheder for behandling er udtømte. Der findes derfor ikke et standardbehandlingsalternativ, og larotrectinib sammenlignes i stedet med placebo eller BSC (se afsnit 6).

Hvis det ikke er muligt at identificere relevante studier, som kan belyse den komparative prognose, vil den kliniske merværdi være vanskelig at kategorisere i henhold til Medicinrådets metoder. Fagudvalget vil i så fald skele til ESMOs vurderingsværktøj *Magnitude of Clinical Benefit Scale* (MCBS – *Form 3*) [11] i vurderingen af larotrectinib.

5.1 Klinisk spørgsmål 1

Hvad er den kliniske merværdi af larotrectinib til behandling af voksne med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

Population
Patienter ≥ 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige acceptable behandlingsmuligheder er udtømte.

Intervention
Larotrectinib.

Komparator
Placebo.

Effektmål
Se tabel 1. Resultaterne præsenteres både for den samlede patientgruppe og for hver af de inkluderede kræftdiagnoser.

5.2 Klinisk spørgsmål 2

Hvad er den kliniske merværdi af larotrectinib til behandling af børn med NTRK-genfusion-positiv kræft, hvor øvrige acceptable behandlingsmuligheder er udtømte, sammenlignet med placebo?

Population
Patienter < 18 år med lokalfremskreden eller metastatisk kræft med NTRK-fusion, hvor alle øvrige acceptable behandlingsmuligheder er udtømte.

Intervention
Larotrectinib.

Komparator
Placebo.

Effektmål
Se tabel 1. Resultaterne præsenteres både for den samlede patientgruppe og for hver af de inkluderede kræftdiagnoser.

5.3 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, den retningsgivende mindste klinisk relevante forskel, en evt. justeret mindste klinisk relevant forskel og kategori. I forbindelse med justeringen af Medicinrådets metodehåndbog, som trådte i kraft pr. 1. januar 2019, vil absolutte effektforskelle fremover blive kategoriseret ud fra konfidensintervaller (tabel 3, side 29 i metodehåndbogen). Det er derfor nødvendigt at foretage en justering af den mindste klinisk relevante forskel. Den *retningsgivende* mindste klinisk relevante forskel er fremkommet på samme måde som under den gamle metode og afspejler den mindste forskel, som, fagudvalget vurderer, er klinisk relevant. Når lægemidlets værdi for det enkelte effektmål skal kategoriseres, vil grænsen for konfidensintervallet blive sammenholdt med den *justerede* mindste klinisk relevante forskel. Den justerede værdi vil være det halve af den retningsgivende værdi i de tilfælde, hvor et konfidensinterval forventes at være tilgængeligt. Rationalet for denne tilgang er at sikre, at alle værdier i konfidensintervallet ligger tættere på den *retningsgivende MKRF* end på 'ingen forskel' (absolut effektforskel på 0). Eller sagt på en anden måde – alle de sandsynlige værdier for effekten er tættere på en klinisk relevant effekt end på 'ingen effekt'.

For alle effektmål ønskes både absolutte og relative værdier, jf. ansøgningsskemaet. Der ønskes både punktestimater og konfidensintervaller (for de absolutte værdier ønskes dog ikke konfidensintervaller, hvor

metoderne til beregning af disse ikke er veldefinerede). For de absolutte værdier, hvor der kan beregnes konfidensintervaller efter veldefinerede metoder, vurderes den kliniske relevans (værdi), jf. tabel 3 i Medicinrådets håndbog for vurdering af nye lægemidler. For de relative værdier vurderes den kliniske relevans (værdi), jf. væsentlighedskriterierne beskrevet i Medicinrådets håndbog. De relative effektestimater skal angives i relativ risiko (RR) eller hazard ratio (HR). Hvis studierne resulterer i en odds ratio (OR), skal denne transformeres til relativ risiko, jf. appendiks 2 i Medicinrådets håndbog. Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Som udgangspunkt vil et onkologisk lægemiddel blive vurderet ud fra, om de resulterer i en forbedring på 10 % for effektmål vedr. effekt og livskvalitet samt en reduktion på 10 % for effektmål vedr. alvorlige bivirkninger for at kunne vurdere, om det giver en klinisk merværdi i forhold til nuværende standardbehandling.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel (retningsgivende og evt. justeret) samt indplacering i de tre kategorier (”dødelighed” ”livskvalitet, alvorlige symptomer og bivirkninger” og ”ikkealvorlige symptomer og bivirkninger”).

Effektmål*	**Vigtighed**	**Effektmålsgruppe**	**Måleenhed**	**Retningsgivende mindste klinisk relevante forskel**
Overlevelse (OS)	*Kritisk*	*Dødelighed/ overlevelse*	Median OS	3 måneder
			OS-rate ved 24 måneder	10 %-point
			Andel patienter med patologisk komplet respons eller radikalt operationsresultat	5 %-point
Livskvalitet	*Kritisk*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Forskel i gennemsnitlig ændring i EORTC-QLQ-C30 (voksne) eller PedsQL (børn)	10 point (QLQ-C30) 4,5 point (PedQL)
Objektiv responsrate (ORR)	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Gennemgang af ORR fordelt på inkluderede kræftdiagnoser	Narrativ gennemgang
Progressionsfri overlevelse (PFS)	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Median PFS *eller* andel progressionsfri patienter ved 12 mdr.	3 mdr. *eller* 10 %-point
Uønskede hændelser	*Vigtig*	*Livskvalitet, alvorlige symptomer og bivirkninger*	Andel patienter, der får én eller flere grad 3-4 AE’s	5 %-point
			Kvalitativ gennemgang af uønskede hændelser	Narrativ vurdering

* For alle effektmål ønskes data med længst mulig opfølgningstid. Desuden ønskes der opgørelser for alle effektmål nævnt i tabellen, dog med undtagelse af bivirkninger, fordelt på hvert af de i larotrectinib-studierne inkluderede kræftdiagnoser.

Kritiske effektmål

Overlevelse

Helbredelse eller forbedret samlet overlevelse (OS) med bedst mulig livskvalitet og mindst mulig toksicitet er det optimale mål for kræftbehandling. For OS anvendes to mål til at vurdere den absolutte effekt: median OS og OS-rate. De to mål supplerer hinanden. Median OS giver svar på, hvornår halvdelen af patientgruppen er død eller forventes at dø. OS-raten giver et estimat for, hvor mange som er i live ved et bestemt tidspunkt. Prognosen for denne gruppe patienter er yderst variabel, da der er tale om vidt forskellige kræfttyper. Overordnet må man dog betragte gruppen som uhelbredeligt syge med en relativt kort gennemsnitlig restlevetid. Fagudvalget vurderer, at begge effektmål for OS er informative. Fagudvalget ønsker derfor at se

på median OS, som kan belyse, hvorvidt halvdelen af patienterne får en overlevelsesgevinst ved behandling med larotrectinib. Den mindste klinisk relevante forskel (MKRF) fastsættes til 3 måneder. For at belyse, hvorvidt behandlingen resulterer i øget langtidsoverlevelse, ønsker fagudvalget at se på OS-raten ved 2 år, som forventes at være lav (< 20 %) for denne gruppe patienter. Her fastsættes den mindste klinisk relevante forskel til 10 %.

Fagudvalget ønsker, som supplement til ovenstående mål, en opgørelse, som omfatter patienter, som enten får patologisk komplet respons (pCR) eller patienter, hvis tumorsvind betyder, at de kan få fjernet deres tumor komplet med frie resektionsrande ved operation (komplet resektion (R0)). Patologisk komplet respons indebærer i tillæg til komplet radiologisk respons også komplet tumorsvind vurderet på operationspræparatet. Fagudvalget vurderer, at denne andel af patienter vil repræsentere patienter, som er helbredte for deres sygdom og dermed har en nær normal forventet restlevetid. Den mindste klinisk relevante forskel fastsættes til 5 %.

Livskvalitet

Livskvalitet er et afgørende helbredsrelateret mål for den enkelte patient. Hos kræftpatienter kan livskvalitet måles med en række forskellige instrumenter, som omfatter både sygdomsspecifikke og generiske værktøjer. I dette tilfælde vil vurdering af livskvalitet hos voksne blive baseret på European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC QLQ-C30) [12,13]. QLQ-C30 er et hyppigt anvendt generisk måleredskab, som består af fem funktionsskalaer, tre symptomskalaer og en 'global' livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. Den mindste klinisk relevante forskel baserer sig på en lille ændring, defineret som 10 point på tværs af domæner [14]. For måling af livskvalitet hos børn og unge findes der ligeledes en række validerede værktøjer. I dette tilfælde vil vurdering af livskvalitet hos børn blive baseret på The Pediatric Quality of Life Inventory (PedsQL) [15], som kan anvendes til børn og unge i alderen 2-18 år. Testen kan enten besvares af børnene selv eller deres forældre. PedsQL består af fire funktionsskalaer med i alt 23 domæner, hvorfra der kan udregnes dels en psykosocial livskvalitetsscore og en fysisk livskvalitetsscore samt en samlet score. Data transformeres til en scoringsskala fra 0-100. Fagudvalget har fastsat den mindste klinisk relevante forskel til 4,5 point jf. litteraturen [16].

Vigtige effektmål

Objektiv responsrate

Objektiv responsrate (ORR) anvendes til belysning af behandlingsrespons og afspejler interventionens umiddelbare antineoplastiske potentiale. Ved vurdering af ORR kategoriserer man ændringer af tumors størrelse efter påbegyndt behandling, jævnfør standardiserede guidelines (Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. Fagudvalget vurderer, at et væsentligt tumorsvind ofte vil bevirke en reduktion i patientens sygdomsbyrde, og at patienter, som ikke modtager aktiv behandling for praktiske formål, vil have en objektiv responsrate på 0 %.

ORR underinddeles i følgende kategorier:

- Komplet respons (CR): Radiologisk kræftfri. Alle tumorlæsioner er væk, og ingen nye er fremkommet.
- Partielt respons (PR): Mindst 30 %-reduktion af tumorlæsioner sammenlignet med baseline.

Objektiv respons (OR) opnås for en patient, hvis vedkommende er klassificeret som CR eller PR, og objektiv responsrate defineres som CR + PR delt med det samlede patientantal.

Fagudvalget vil vurdere den samlede andel af patienter, som opnår OR, samt andelene af patienter, som opnår CR eller PR. I studierne af larotrectinib er der inkluderet patienter på tværs af mange kræftdiagnoser, og for flere af disse subgrupper indgår der kun ganske få patienter, hvilket medfører betydelig usikkerhed omkring resultaterne. Fagudvalget finder derfor, at det er mest hensigtsmæssigt at foretage en narrativ vurdering af resultaterne for ORR inden for hver enkelt kræftdiagnose. Fagudvalget ønsker, som angivet i tabel 1, resultater fordelt på hvert af de i larotrectinib-studierne inkluderede kræftdiagnoser.

Progressionsfri overlevelse

PFS bliver anvendt til at vurdere, hvor lang tid der går, inden sygdommen udvikler sig. PFS er defineret som tiden fra randomisering til første dokumentation af sygdomsprogression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [18] eller dødsfald.

Fagudvalget vurderer, at det er vigtigt for patienterne ikke at have sygdomsprogression i længst mulig tid. Patienter med sygdomsprogression kan have meget generende symptomer, og den aktuelle patientgruppe har ingen efterfølgende behandlingsalternativer. Fagudvalget betragter PFS som et vigtigt effektmål. PFS er i dette tilfælde ikke et surrogat for overlevelse men er derimod et udtryk for fravær eller reduktion af symptomer og for varighed af respons.

Der er væsentlige forskelle i prognose på tværs af forskellige kræfttyper med NTRK-genfusion. Larotrectinib er indiceret til lokalavanceret eller metastatisk kræft, når øvrige acceptable behandlingsmuligheder er udtømte. Derfor vurderer fagudvalget, at patientgruppen generelt vil have en relativt kort tid til sygdomsprogression. På den baggrund fastsættes den mindste klinisk relevante forskel som 3 måneder (vedr. median PFS) eller 10 %-point (vedr. PFS-rate ved 12 måneder). Fagudvalget vil i sin vurdering prioritere effektmålet opgjort som forskel i median PFS over andel patienter, der er progressionsfri efter 12 måneder.

Uønskede hændelser

Forekomst af uønskede hændelser grad 3-4 er et udtryk for alvorlig toksicitet af lægemidlet [19], og disse kan have væsentlig indvirkning på patienternes velbefindende. Da larotrectinib skal anvendes til behandling af uhelbredeligt syge patienter, som forventes at dø af deres sygdom, vurderes det, at uønskede hændelser er et vigtigt effektmål. Fagudvalget ønsker data på nedenstående måleenheder.

<u>Uønskede hændelser grad 3-4</u>
Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [19].

Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får bivirkninger af grad 3-4, er klinisk relevant.

<u>Kvalitativ gennemgang af uønskede hændelser</u>
Ansøger skal indsende en opgørelse for frekvensen af alle uønskede hændelser. Fagudvalget ønsker at foretage en gennemgang af alle uønskede hændelser, der opstår ved behandling med larotrectinib versus komparator med henblik på at vurdere hændelsernes type, håndterbarhed og reversibilitet.

6 Litteratursøgning

Vurderingen af klinisk merværdi baseres som udgangspunkt på data fra peer-reviewede publicerede fuldtekstartikler og data fra EMAs EPAR – public assessment report(s). Data skal derudover stemme overens med protokollens beskrivelser.

Sekretariatet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere peer-reviewede publicerede fuldtekstartikler, hvor larotrectinib er sammenlignet direkte med komparator (placebo eller BSC).

Sekretariatet har ikke fundet artikler, som kan anvendes til direkte sammenligning af larotrectinib og placebo eller BSC.

Virksomheden skal derfor søge efter studier, der kan anvendes til en indirekte sammenligning af larotrectinib og placebo eller BSC. Det betyder, at der både skal søges efter primærstudier af larotrectinibs effekt og efter primærstudier af effekten af placebo eller BSC. Til det formål har sekretariatet udarbejdet søgestrenge, som skal anvendes i MEDLINE (via PubMed) og CENTRAL (via Cochrane Library). Søgestrengene kan findes i Bilag 1. Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Kriterier for udvælgelse af litteratur
Virksomheden skal først ekskludere artikler på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Søgestrategi og studiedesigns: der skal foretages en trinvis søgning efter data vedr. effekten af komparator, som kan tillade en naiv sammenstilling. Der skal først søges efter et eller flere RCTs med en studiepopulation, som i tilstrækkeligt omfang afspejler de patienter, som indgår i udviklingsprogrammet for larotrectinib. Herunder studier, hvor én eller flere af kræftdiagnoserne, som indgår, også er repræsenteret i studierne af larotrectinib. Hvis der ikke findes relevant data fra RCTs søges dernæst efter observationelle studier.

Prioritet søgestrategi

1. RCT-data for patienter med NTRK-fusion (se søgestrenge i Bilag 1)
2. Observationelt data for patienter med NTRK-fusion (se søgestrenge i Bilag 1)
3. RCT-data for patienter uden kendt NTRK-status (se søgestrenge i Bilag 2)

For ovenstående gælder det, at populationen i videst muligt omfang skal svare til studiepopulationen, der indgik i larotrectinibs udviklingsprogram. Findes der ikke relevante RCT-data ved søgning med søgestreng i Bilag 1, gennemgås derpå de observationelle søgeresultater og dernæst anvendes søgestrenge i Bilag 2. Data fra en evt. placebogruppe prioriteres over data for BSC.

7 Databehandling og analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelige for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risikoreduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end ét sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (meta-analyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

8 Andre overvejelser

Fagudvalget skønner, at datagrundlaget for vurderingen kan være begrænset grundet den vævsagnostiske indikation og designet af de studier, der ligger til grund for EMAs vurdering af larotrectinib [10].

Fagudvalget ønsker en opgørelse, som sammenligner PFS og ORR-data for den behandling, patienterne modtog i behandlingslinjen umiddelbart inden behandling med larotrectinib versus tilsvarende data for behandling med larotrectinib (også kaldet *'Growth modulation index'*).

Fagudvalget vurderer, at der er væsentlige udfordringer i relation til hensigtsmæssig screening for NTRK-fusion. Derfor bedes ansøger redegøre for, hvor mange patienter, som det estimeres, skal screenes for at identificere ca. 30 patienter (ansøgers eget skøn for antallet af patienter, der årligt vil kunne behandles med larotrectinib i Danmark), samt et bud på hvilke kræftdiagnoser som bør screenes. Fagudvalget beder også virksomheden oplyse hvilke(n) konkret(e) metode(r) til screening af NTRK-fusion, der vurderes at være bedst, og hvorvidt der evt. skal præ-screenes f.eks. med IHC forud for mere avancerede metoder med højere sensitivitet såsom NGS. Endeligt bør ansøger komme med et bud på, hvornår i udrednings- og/eller behandlingsforløb screening for NTRK-fusion bør foregå.

Ansøger bedes indsende evt. litteratur, som belyser den prognostiske betydning af NTRK-fusion.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende tværgående kræftlægemidler

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11 Versionslog

Version	Dato	Ændring
1.0	19. februar 2020	Godkendt af Medicinrådet.

12 Bilag 1

Søgestreng for identifikation af RCTs og observationelle studier i PubMed. Patienter med NTRK-fusion.

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	larotrectinib[nm]	Søgetermer for intervention
2	larotrectinib[tiab] OR Vitrakvi*[tiab] OR ARRY-470[tiab] OR LOXO-101[tiab]	
3	(NTRK[tiab] OR NTRK1[tiab] OR NTRK2[tiab] OR NTRK3[tiab]) AND (fusion[tiab] OR fusions[tiab])	Søgetermer for patienter med NTRK fusion
4	neurotrophi*[tiab] AND (TRK[tiab] OR TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab]) AND (fusion[tiab] OR fusions[tiab])	
5	neurotrophi*[tiab] AND tropomyosin receptor kinase*[tiab] AND (fusion[tiab] OR fusions[tiab])	
6	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND positive[tiab]	
7	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND proteins[tiab]	
8	TRK[tiab] AND (fusion[tiab] OR fusions[tiab]) AND (cancer[tiab] OR cancers[tiab])	
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	
10	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR review[ti]	Eksklusion af ikke relevante publikationstyper
11	#9 NOT #10	
12	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR Clinical Trials as Topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh])	RCT filter
13	**#11 AND #12**	**Endelig søgning RCT**
14	Observational Study[pt] OR Epidemiologic Studies[mh:noexp] OR Case Control Studies[mh] OR Cohort Studies[mh] or Cross-Sectional Studies[mh]	Søgefilter til identifikation af observationelle studier
15	observational[tiab] OR case control[tiab] OR cohort[tiab] OR cohorts[tiab] OR follow-up[tiab] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab] OR cross sectional[tiab]	
16	#14 OR #15	
17	#11 AND #16	**Endelig søgning på observationelle studier** inkl. eksklusion af tidligere screenede RCTs
18	**#17 NOT #13**	

Søgestreng for identifikation af RCTs og observationelle studier i CENTRAL (Cochrane Library). Patienter med NTRK-fusion.

https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
1	larotrectinib:kw	Søgetermer for intervention
2	(larotrectinib OR "ARRY 470" OR "LOXO 101"):ti,ab	
3	((NTRK OR NTRK1 OR NTRK2 OR NTRK3) NEAR/5 (fusion OR fusions)):ti,ab	Søgetermer for patienter med NTRK fusion
4	neurotrophi*:ti,ab AND (TRK OR TRKA OR TRKB OR TRKC):ti,ab AND (fusion OR fusions):ti,ab	
5	neurotrophi*:ti,ab AND (tropomyosin NEXT receptor NEXT kinase*):ti,ab AND (fusion OR fusions):ti,ab	
6	TRK:ti,ab AND (fusion OR fusions):ti,ab AND positive:ti,ab	
7	TRK:ti,ab AND (fusion OR fusions):ti,ab AND proteins:ti,ab	
8	TRK:ti,ab AND (fusion OR fusions):ti,ab AND (cancer OR cancers):ti,ab	
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	
10	("conference abstract" OR review):pt	Eksklusion af ikke relevante publikationstyper
11	NCT*:au	
12	("clinicaltrials.gov" OR trialsearch):so	
13	#10 OR #11 OR #12	
14	**#9 NOT #13**	**Endelig søgning**

13 Bilag 2

Søgestreng for identifikation af RCTs i PubMed. Patienter med ukendt NTRK-status.

https://www.ncbi.nlm.nih.gov/pubmed/advanced

#	Søgetermer	Kommentar
1	solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour[ti] OR tumours[ti])	Søgetermer for tumortyper
2	(soft tissue[ti] OR soft-part[ti] OR connective tissue[ti]) AND (sarcoma[ti] OR sarcomas[ti] OR cancer[ti] OR cancers[ti])	
3	angiosarcoma[ti] OR hemangiosarcoma[ti] OR chondrosarcoma[ti] OR fibromyxosarcoma[ti] OR fibrosarcoma[ti] OR infantile fibrosarcoma[ti] OR myxofibrosarcoma[ti] OR leiomyosarcoma[ti] OR liposarcoma[ti] OR malignant mesenchymoma[ti] OR malignant mesenchymal tumor[ti] OR neurofibrosarcoma[ti] OR rhabdomyosarcoma[ti] OR synovial sarcoma[ti] OR spindle cell sarcoma[ti]	
4	bone cancer[ti] OR bone sarcoma[ti] OR Ewing sarcoma[ti] OR osteosarcoma[ti]	
5	MASC[ti] OR mammary analogue secretory carcinoma[ti]	
6	(salivary[ti] OR parotid[ti] OR submandibular[ti] OR sublingual[ti]) AND (gland[ti] OR glands[ti]) AND (masc[ti] OR cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
7	(bowel[ti] OR colon[ti] OR colonic[ti] OR colorectal[ti] OR rectal[ti] OR rectum[ti] OR sigmoid[ti] OR intestinal[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
8	(thyroid[ti] OR parathyroid[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
9	gastrointestinal stromal[ti] AND (tumor[ti] OR tumour[ti] OR tumors[ti] OR tumours[ti])	
10	GIST[ti]	
11	lung[ti] AND (adenocarcinoma[ti] OR carcinoma[ti])	
12	NSCLC[ti] OR non-small cell lung cancer[ti] OR nonsmall cell lung cancer[ti]	
13	melanoma[ti]	
14	cholangiocarcinoma[ti]	
15	(bile duct*[ti] OR biliary duct*[ti]) AND (carcinoma[ti] OR cancer[ti])	
16	(appendiceal[ti] OR appendix[ti]) AND (cancer[ti] OR carcinoma[ti])	
17	breast[ti] AND secretory[ti] AND (carcinoma[ti] OR carcinomas[ti])	
18	congenital mesoblastic nephroma[ti]	
19	(pancreatic[ti] OR pancreas[ti]) AND (cancer[ti] OR carcinoma[ti] OR adenocarcinoma[ti])	
20	primary[ti] AND (CNS[ti] OR central nervous system[ti] OR brain[ti]) AND (cancer[ti] OR tumour[ti] OR tumor[ti] OR lymphoma[ti])	
21	glioblastoma[ti] OR glioma[ti] OR astrocytoma[ti] OR oligodendroglioma[ti] OR primary cerebral lymphoma[ti]	

22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
23	metastatic[ti] OR metastasis[ti] OR metastases[ti] OR advanced[ti] OR recurrent[ti] OR refractory[ti]	Søgetermer for avanceret/metastatisk sygdom
24	treatment resistant[tiab] OR treatment resistance[tiab] OR chemotherapy resistant[tiab]	Søgetermer for patientstadie
25	incurable[tiab] OR "no cure"[tiab] OR untreatable[tiab]	
26	late stage[tiab]	
27	Terminally Ill[mh] OR Terminal Care[mh] OR (terminal[tiab] NOT terminal half-life[tiab]) OR terminally[tiab]	
28	best supportive care[tiab] OR active supportive care[tiab] OR optimal supportive care[tiab] OR supportive care alone[tiab] OR supportive care only[tiab]	
29	symptomatic treatment[tiab] OR symptomatic therapy[tiab] OR experimental treatment[tiab] OR late-line[tiab]	
30	Palliative Care[mh] OR palliation[tiab] OR palliative[tiab] OR palliatively[tiab]	
31	eol care[tiab] OR end of life[tiab]	
32	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	
33	#22 AND #23 AND #32	
34	(Randomized Controlled Trial[pt] OR Controlled Clinical Trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[ti]) NOT (Animals[mh] NOT Humans [mh])	RCT filter
35	English[la]	Sproglig afgrænsning
36	#33 AND #34 AND #35	
37	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR Meta-Analysis[pt] OR News[pt] OR Observational Study[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti] OR meta-analysis[tiab] OR review[ti] OR Retrospective Studies[mh] OR retrospective[ti] OR systematic review[tiab]	Eksklusion af irrelevante publikationstyper
38	**#36 NOT #37**	**Endelig søgning**

Søgestreng for identifikation af RCTs i CENTRAL (referencer fra Embase). Patienter med ukendt NTRK-status.

https://www.cochranelibrary.com/advanced-search/search-manager

#	**Søgetermer**	**Kommentar**
1	solid:ti AND (tumor OR tumors OR tumour OR tumours):ti	Søgetermer for tumortyper
2	(soft tissue OR soft-part OR connective tissue):ti AND (sarcoma OR sarcomas OR cancer OR cancers):ti	
3	(angiosarcoma OR hemangiosarcoma OR chondrosarcoma OR fibromyxosarcoma OR fibrosarcoma OR infantile fibrosarcoma OR myxofibrosarcoma OR leiomyosarcoma OR liposarcoma OR "malignant mesenchymoma" OR "malignant mesenchymal tumor" OR	

	neurofibrosarcoma OR rhabdomyosarcoma OR synovial next sarcoma OR spindle next cell next sarcoma):ti	
4	(bone next cancer OR bone next sarcoma OR "Ewing sarcoma" OR osteosarcoma):ti	
5	(MASC OR "mammary analogue secretory carcinoma"):ti	
6	(salivary OR parotid OR submandibular OR sublingual):ti AND (gland OR glands):ti AND (masc OR cancer OR carcinoma OR adenocarcinoma):ti	
7	(bowel OR colon OR colonic OR colorectal OR rectal OR rectum OR sigmoid OR intestinal):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	
8	(thyroid OR parathyroid):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	
9	"gastrointestinal stromal":ti AND (tumor OR tumour OR tumors OR tumours):ti	
10	GIST:ti	
11	lung:ti AND (adenocarcinoma OR carcinoma):ti	
12	(NSCLC OR "non-small cell lung cancer" OR "nonsmall cell lung cancer"):ti	
13	melanoma:ti	
14	cholangiocarcinoma:ti	
15	(bile next duct* OR biliary next duct*):ti AND (carcinoma OR cancer):ti	
16	(appendiceal OR appendix):ti AND (cancer OR carcinoma):ti	
17	breast:ti AND secretory:ti AND (carcinoma OR carcinomas):ti	
18	congenital next mesoblastic next nephroma:ti	
19	(pancreatic OR pancreas):ti AND (cancer OR carcinoma OR adenocarcinoma):ti	
20	primary:ti AND (CNS OR "central nervous system" OR brain):ti AND (cancer OR tumour OR tumor OR lymphoma):ti	
21	(glioblastoma OR glioma OR astrocytoma OR oligodendroglioma OR "primary cerebral lymphoma"):ti	
22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
23	(metastatic OR metastasis OR metastases OR advanced OR recurrent OR refractory):ti	Søgetermer for avanceret/metastatisk sygdom
24	((treatment OR chemotherapy) next (resistant OR resistance)):ti,ab	Søgetermer for patientstadie
25	(incurable OR "no cure" OR untreatable):ti,ab	
26	late-stage:ti,ab	
27	("Terminally Ill" OR "Terminal Care" OR "terminal disease"):kw OR (terminal OR terminally):ti,ab	
28	("best supportive care" OR "active supportive care" OR "optimal supportive care" OR "supportive care alone" OR "supportive care only"):ti,ab	
29	((symptomatic OR experimental) next (treatment OR therapy)):ti,ab OR "late-line":ti,ab	
30	(palliation OR palliative OR palliatively):ti,ab,kw	
31	("eol care" OR "end of life"):ti,ab	
32	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	
33	#22 AND #23 AND #32	

34	("conference abstract" OR review OR meta-analysis):pt	Eksklusion af irrelevante publikationstyper
35	NCT*:au	
36	("clinicaltrials.gov" or trialsearch):so	
37	(abstract OR review):ti	
38	#34 OR #35 OR #36 OR #37	
39	#33 NOT #38	
40	Embase:an NOT Pubmed:an	Afgrænsning til poster fra Embase
41	#39 AND #40	**Endelig søgning**